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GASTROENTEROLOGY

Official Journal of the American Gastroenterological Association

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A list of forthcoming articles will be found in the advertising section following the ABSTRACTS

VOLUME 1, NUMBER 1

GASTROENTEROLOGY

Official Journal of the American Gastroenterological Association

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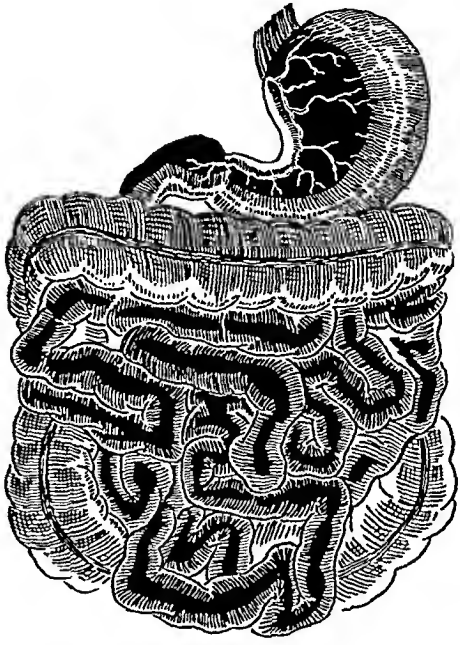
Tranquillity

OF THE G. I. TRACT



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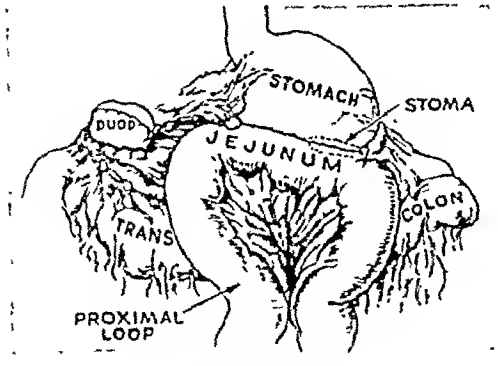
These striking results led to the successful use of Phosphaljel in the treatment of peptic ulcer in man and disclosed its special usefulness in those cases of peptic ulcer associated with a relative or absolute deficiency of pancreatic juice, diarrhea or a low phosphorus diet.[1]

GASTROJEJUNAL ULCER. Most difficult of all to treat satisfactorily—are gastrojejunal ulcers[2]. In these highly resistant lesions Phosphaljel has been found to be effective. Gastrojejunal ulcers may occur after surgical procedures such as that shown below.



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1. *Tanley, G. B.; Freeman, S.; Ivy, A. C.; Atkinson, A. J.; and Wigodsky, H. S.;* Aluminum Phosphate in the Therapy of Peptic Ulcer, Arch. Int. Med. 67, 563-578 (March) 1941.
2. *Marshall, S. F., and Devine, J. W., Jr.;* Gastrojejunal Ulcer, S. Clin. North America, 743-761 (June) 1941.

*Reg. U. S. Pat. Off.

JOHN WYETH & BROTHER, INCORPORATED, PHILADELPHIA

PREPYLORIC LESIONS OF THE STOMACH: MEDICAL AND SURGICAL ASPECTS

SARA M. JORDAN, M.D., AND FRANK H. LAHEY, M.D.

The Lahey Clinic, Boston

The prepyloric part of the stomach has extraordinary interest for both diagnostician and pathologist, for it may be the site of the most baffling abnormalities. The normal function of the pylorus involves powerful contractions and a certain degree of relaxation of a strong muscular ring. These contractions may be excessive, continuous and habitual, and result in an intermittent state of spasm which may seriously confuse the diagnostician. The symptoms of such spasm and the radiologic picture of constriction and rigidity of the prepyloric part of the stomach may strongly suggest organic disease. Furthermore, there may even be an actual thickening of the muscle to such a degree as to simulate a neoplasm both radiologically and on exploration to the examining fingers of the surgeon.

The pylorus is notoriously a prominent effector zone for impulses arising from the hypothalamus, its contraction reflecting nervous states and emotional traumas. This is frequently demonstrated by the symptoms of pylorospasm: "the lump in the stomach," nausea and vomiting. In the large group of persons who react to life via the pylorus, spasm in the pyloric and prepyloric area of the stomach is a frequent occurrence. When the constriction is sufficiently great and enduring, it may be habitual and result in symptoms which simulate ulcer or neoplasm and findings in the roentgenogram which are often indistinguishable from those of an organic lesion.

Spasm alone, without the resultant thickening and inflexibility of the pyloric and prepyloric muscle, may be relieved by antispasmodic measures of two types. The first type is practicable when spasm is nonhabitual and not severe, and consists of the usual drugs such as atropine, and still more effectively of a psychologic measure which we have practiced for many years, namely, a casual conversation with the patient during fluoroscopy concerning food delicacies. The resulting mental picture produces vigorous active peristalsis in the media and antrum and relaxation of the pylorus. Many recalcitrant stomachs have yielded gracefully to this persuasion, especially when the conversation is gently and not too pointedly introduced. The second type of antispasmodic measure is practicable when spasm has existed for a long time and has resulted in some thickening of the muscle. In these cases, bed rest and treatment, such as are used in actual ulcer, are necessary to produce a gradual relaxation which is adequate for differentiation from

an organic lesion. In many of these cases, the presence of hyperchlorhydria and the character of the symptoms are so suggestive of ulcer that intensive treatment is necessary. Relief of symptoms is sometimes, but not always, attended by relief of spasm, and in these cases no defect, either crater or irregularity of the mucosal pattern, is demonstrated at any time during treatment. It has therefore been assumed that habitual pylorospasm alone has been the cause of the symptoms. However, since the routine use of the gastroscope, so many small shallow ulcers of the gastric mucosa have been visualized throughout the walls of the stomach that we are inclined to believe that such small ulcers, though not visualized radiologically, are often present in this type of case and cause the spasm and hyperchlorhydria and are healed by the treatment.

In certain of these cases, intensive ulcer treatment may relieve the symptoms completely, but the prepyloric constricting defect persists unchanged. Gastroscopic visualization may reveal a completely normal mucosa, but leave the suspicion of an intramural lesion. In certain cases, because of the persistently existing spasm, it may be impossible to be certain that the stomach walls down to the sphincter are actually visualized. In such cases, adequate trial therapy is used to prove the benignancy of the lesion by three critera: disappearance of symptoms, occult blood in the stools, and the roentgenologic defect. In these cases the last of these criteria has not been fulfilled, therefore the only alternative is to advise surgical exploration.

A certain number of such cases have no abnormality discernible to the eye and the hand of the surgeon, the rest being divided among (1) those having thickened muscularis, (2) those with definite gastritis, (3) those with a small mucosal ulcer with or without gastritis, and (4) those with a malignant lesion, usually an infiltrating carcinoma. The patients in the last three groups, those with actual lesions, should, of course, have exploration and resection—the carcinoma for obvious reasons, the unhealed chronic gastritis and the shallow unhealed ulcer because it is reasonable to assume that in a part of the body as susceptible to malignancy as the stomach, any unhealed pathologic condition might be a precursor of malignancy. Even an entirely benign, localized, chronic gastritis is now under suspicion of potentiality of later malignancy.

There can be only complete satisfaction with the early discovery of a malignant lesion, and certainly no regret for the resection of a potentially malignant condition, such as unhealed ulcer or localized prepyloric chronic gastritis. Furthermore, under the circumstances described above, there should be no regret for an exploration which shows either no pathologic condition in the stomach, or a thickened muscularis which can be identified as such by the surgeon. In both these types of cases, the stomach may be left intact and the patient may be given complete reassurance. There is no regret for the

exploration because every preoperative procedure has been conscientiously used to differentiate between an actual and a phantom lesion. The intelligent patient can be so instructed preoperatively in the details of the situation that he accepts either positive or negative findings, and even in distant retrospect regards the "necessary" exploration as justified and reassuring. The less

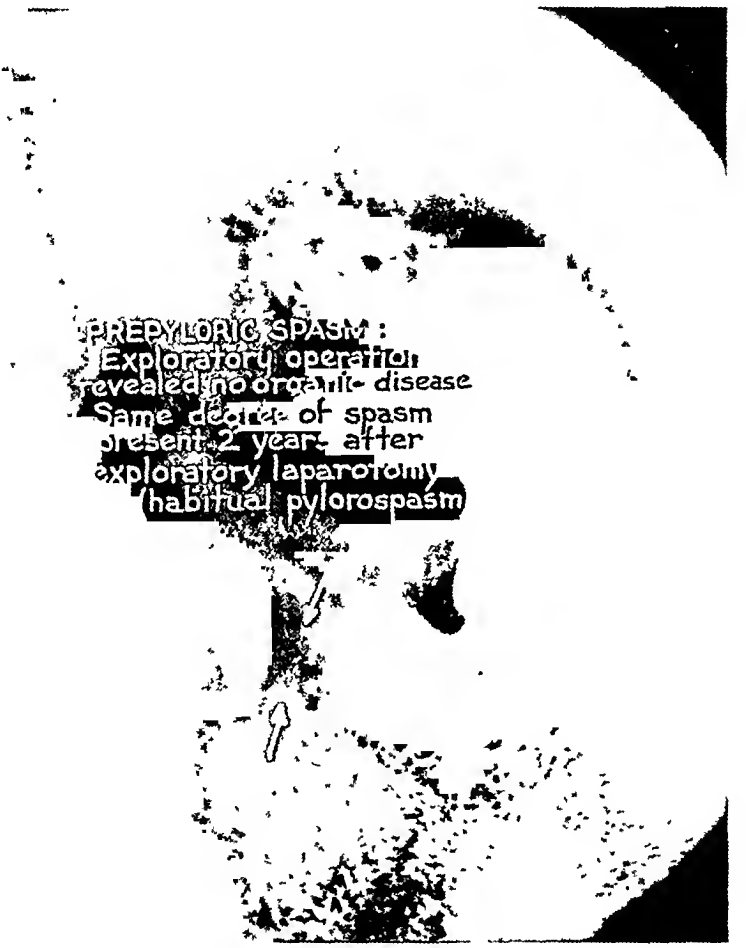

FIG 1 CASE 1

intelligent and cooperative patient may well think and comment unfavorably upon the operative procedure, regarding it as unnecessary, especially at a later date, but this possible future mental inadequacy of the patient cannot deter the gastro-enterologist or the surgeon from advising exploration when there is a medically reasonable doubt as to the presence of a malignant or potentially malignant lesion

In cases 1 and 2, it was our opinion that there had been an ulcer at the

pylorus which, because of the thickening of the muscularis, was not visualized radiologically or palpated by the surgeon. Case 1 (fig. 1), a man aged 60 years, had a strong family history of carcinoma of the stomach, with a history of gastric ulcer of five years' duration, hemorrhage, loss of twelve pounds in weight and symptoms of exhaustion, and showed an achlorhydria

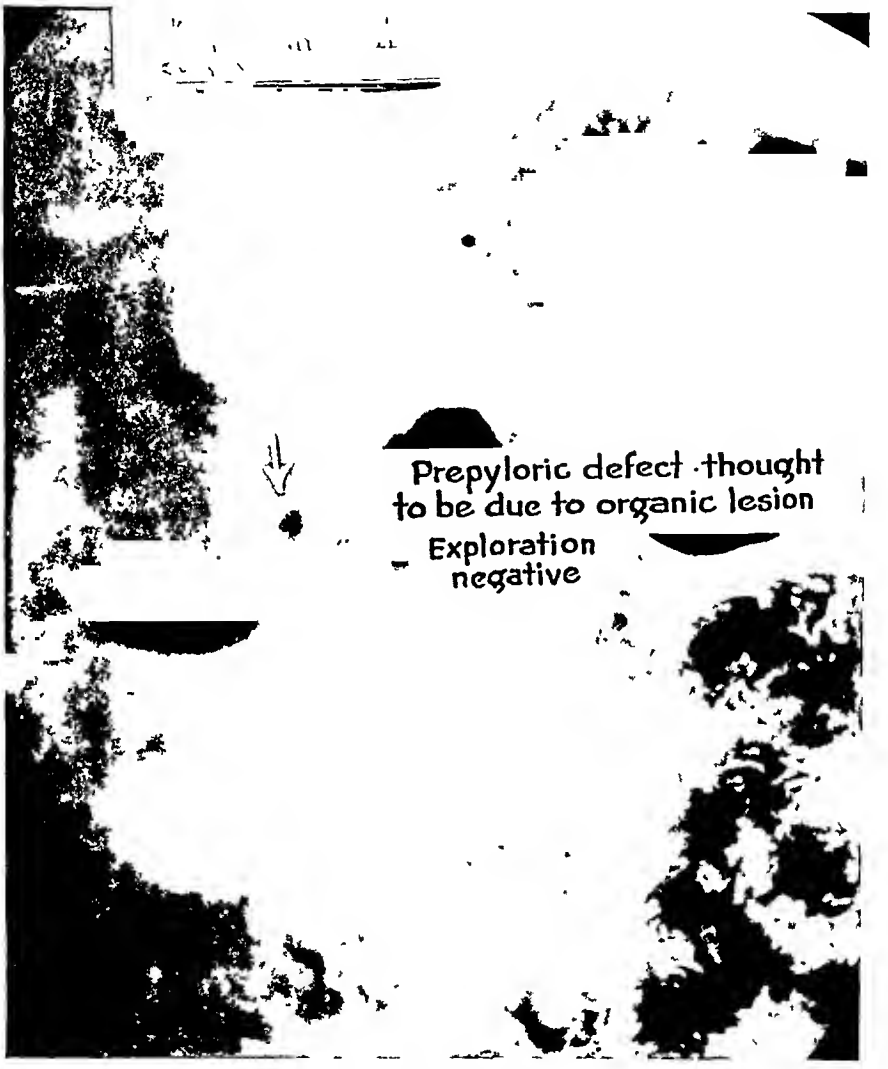

Fig 2. Case 2

and a constricting defect of the antrum. On exploration, thickening of the pyloric ring was found, but careful examination failed to reveal any lesion. The patient is well now, two and a half years postoperatively. Case 2 (fig 2), a man aged 57 years, had a somewhat similar history, but with hyperchlorhydria. A longer postoperative history (seven years) included recurrence of ulcer symptoms and a constantly persistent defect on roentgeno-

logic examination annually for seven years. The exploratory operation seven years ago revealed no organic lesion.

Another interesting case which demonstrated the difficulty of finding a healing or healed ulcer at the pylorus even by surgical palpation, was that of a male of 41 years, who was first seen in 1939 with a history of loss of weight (40 pounds in eleven months), heartburn, belching, nausea and vomiting, and epigastric pain. Roentgenologic examination showed a prepyloric defect. There was free acid of 45. The prepyloric defect persisted under treatment. Gastroscopy showed pylorospasm with questionable ulcer. Exploration showed only spasm of a thickened pylorus and prepyloric area. Two years later he returned with recurrent symptoms, this time with achlorhydria. Exploration was again undertaken and an irregular mass, thought to be an adenomatous polyp, was found. Resection was carried out and microscopic diagnosis showed chronic gastritis with a faint puckering of the mucosa with slight induration suggesting healed ulcer. The muscularis of the pyloric ring and antral portion was thickened up to 0.7 cm.

Causes of prepyloric spasm extrinsic to the prepyloric area itself must be sought in all cases in which no local cause is found. It is, of course, well known that an ulcer elsewhere in the stomach, particularly one of the posterior wall near the lesser curvature, may produce so much gastric irritation that habitual pyloric and prepyloric spasm occurs. Certain of these posterior wall ulcers are difficult to find roentgenologically; the crater may fill fluoroscopically or by film examination only when the patient is in the supine position. In such cases, the prepyloric constricting deformity, however persistent it may be at first, disappears with successful treatment of the ulcer. In some of these cases, it is very possible that the actual causative lesion may never be visualized or even suspected, for if the ulcer is shallow, it may not be detected when it exists, and it may heal so rapidly that its presence is never suspected. A gastric ulcer in the prepyloric area or involving the pylorus itself is often difficult to visualize, and if on the posterior wall is, like that of the rest of the stomach, found only with careful palpation under the fluoroscope with the patient in the supine position. The so-called spot film taken during fluoroscopic observations, may indicate the size of the lesion, and similar later check-up examinations show the reduction in size and final disappearance of the ulcer. It is especially important that lesions in this area be followed to complete healing, for although there is now no longer any doubt that benign ulcers occur and can be healed in the prepyloric part of the stomach, this is also a fertile ground for carcinoma, the early detection of which is especially promising where, as in this area, resection can be easily done.

The ulcer directly in the pylorus or extending into the duodenum, or even the duodenal ulcer, may at times produce so rigid a constriction that the pre-

operative diagnosis of carcinoma is very definitely made. Case 3 (fig. 3), a male of 58 years, had symptoms of epigastric distress, somewhat relieved by food, of six weeks' duration. Stools were thought by the patient to be black at the onset of symptoms. There was no loss of weight or a pal-

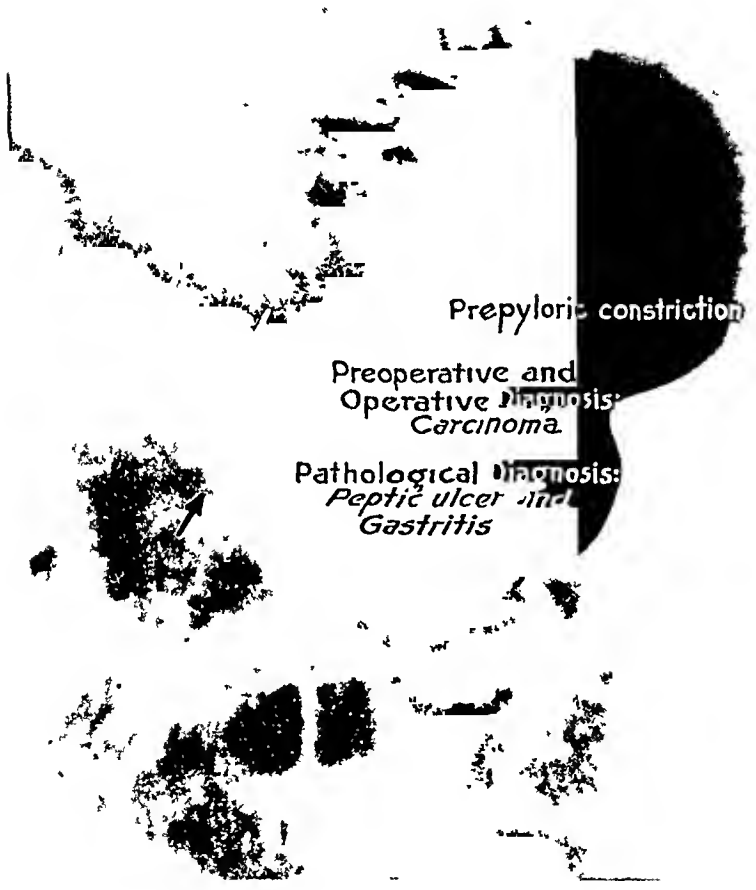

FIG 3 CASE 3

pable mass An achlorhydria and slight anemia were found, together with a constantly constricted antrum through which no transmission of peristaltic waves was observed The short history, achlorhydria, and prepyloric constriction all pointed so definitely to the diagnosis of carcinoma that operation was advised at once The surgeon on palpation found the prepyloric stomach to be markedly firm and had no reason for doubting the diagnosis, but the

pathologist found a punched-out ulcer 1 cm. in diameter and 0.5 cm. deep, situated in the pylorus, and extending into the duodenum, and a soft ovoid elevation of mucosa 1.3 cm. in diameter and 0.6 cm. in maximum height. The muscularis in the antral region was thickened and reached a maximum of 1.2 cm. at the pyloric ring. His diagnosis was chronic peptic ulcer and chronic

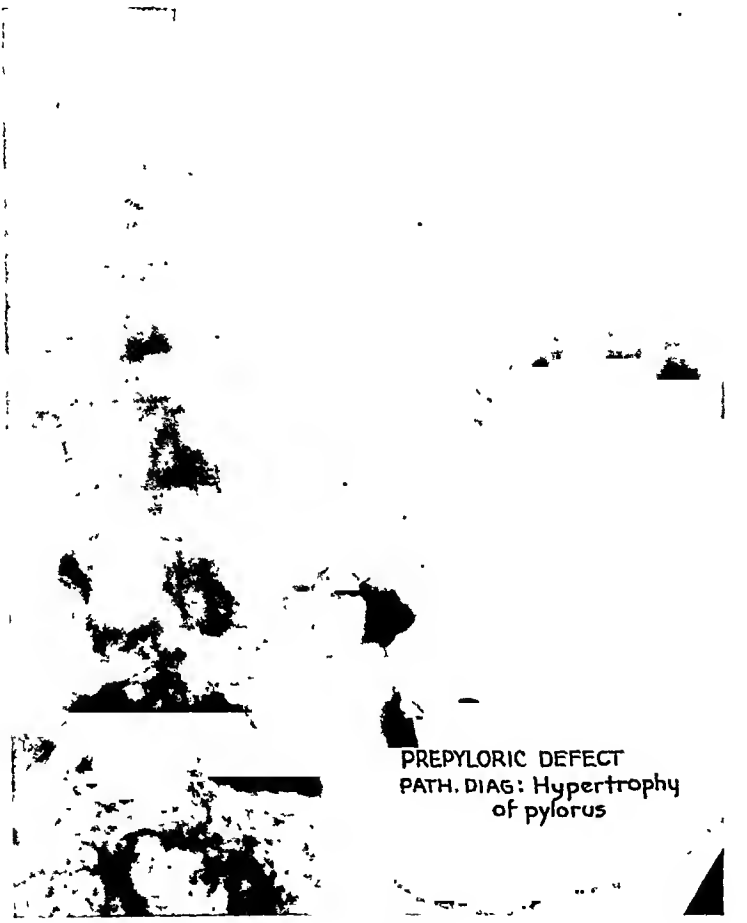

FIG. 4. CASE 4

gastritis. The patient made an excellent recovery and is well now, four months after operation. It is our belief that the finding of chronic gastritis at this site and the resection of the affected area may well have prevented the development of a later malignancy.

Case 4 (fig. 4) is similar except that in this case the patient was at first suspected of having a prepyloric gastric ulcer, but upon exploration

because of a persistent prepyloric defect, no lesion except thickening and edema of the prepyloric area was found. The pathologic diagnosis of excised lymph nodes was hyperplasia of the nodes. Gastroscopy failed to visualize the prepyloric area, but showed evidence of gastritis in the media of the stomach.

Completely extragastric conditions may produce temporary or habitual pylorospasm, such conditions as recurrent appendicitis, gallbladder disease, colonic dysfunction, and even conditions outside the gastro-intestinal tract, notably renal calculi, migraine and cardiac disease. Habitual pylorospasm in such cases may be visualized in a routine gastro-intestinal survey, or in one specially indicated because of symptoms resulting from pylorospasm. In either case, a suspicion of gastric malignancy, arising from the roentgenogram and unchecked by further study of the patient, may divert attention from the underlying cause and the true diagnosis.

Case 5 (fig. 5), a male aged 67 years, had symptoms and roentgenologic evidence of pylorospasm which made a gastro-intestinal survey necessary and the diagnosis of an organic lesion possible, but the final diagnosis was aortic stenosis with decompensation, the gastric symptoms and roentgenologic defect being secondary conditions.

Prepyloric constriction is sometimes produced by previous operation and in the presence of symptoms, may produce confusion in diagnosis. Case 6 (fig. 6), a male aged 56 years, had a pyloroplasty for suspected malignancy five years before admission. The pathologic diagnosis was hypertrophic pylorus. Roentgenologic examination showed postoperative deformity of the prepyloric area. This patient's symptoms were due to colonic spasm and pylorospasm and were relieved by treatment directed toward relief of functional disturbances.

There is hardly a surgeon who has had a large experience with the surgical problems of peptic ulcer and gastric malignancy who has not been faced with the difficulty associated with prepyloric lesions. As has already been stated in Dr. Jordan's section of this paper, certainly one of the most difficult problems is the one of the patient and his relatives when in the presence of a persistent prepyloric defect exploration has been undertaken with negative findings. Personally I have had this experience four or five times, and I concur with Dr. Jordan's statement that the most important feature is frank discussion of the entire problem with the patient and his family if one wishes to avoid criticism and suspicion that adequate measures were not taken preoperatively to determine the absence of malignancy.

As I have observed these cases with the Department of Gastro-Enterology and have helped make the decision in favor of exploratory operation, I am certain that there are prepyloric defects as demonstrated by roentgenogram

that cannot be made to disappear by any known drug or plan of treatment. This being the situation, to find no lesion at exploratory operation when the roentgenologic defect is probably due to prepyloric spasm is definitely better

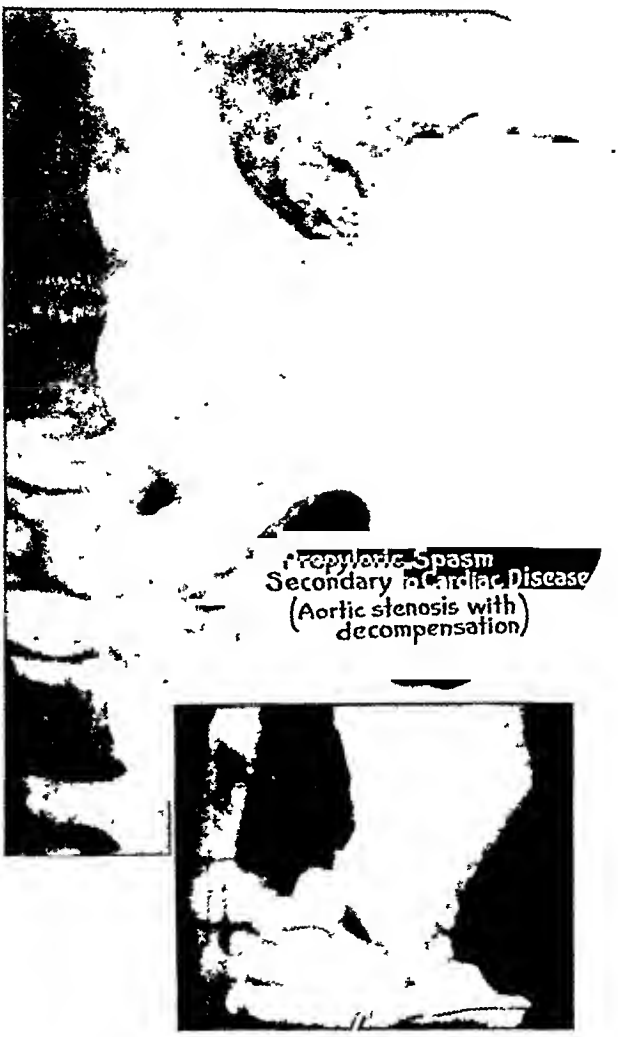

FIG 5 CASE 5

than at a later date to find that the lesion is malignant and that the favorable time for removal has passed This is too high a price to pay for a simple exploration. Each time that we have performed such an exploration and found an early lesion, we have been rewarded by a feeling of gratifying satisfaction. In the few cases in which we have explored such a lesion with negative

findings, my conscience has been utterly clear and the reward of being sure has been well worth while.

In order, however, that others may know what we have been through with patients, I must add that in spite of warning the patient and his family that

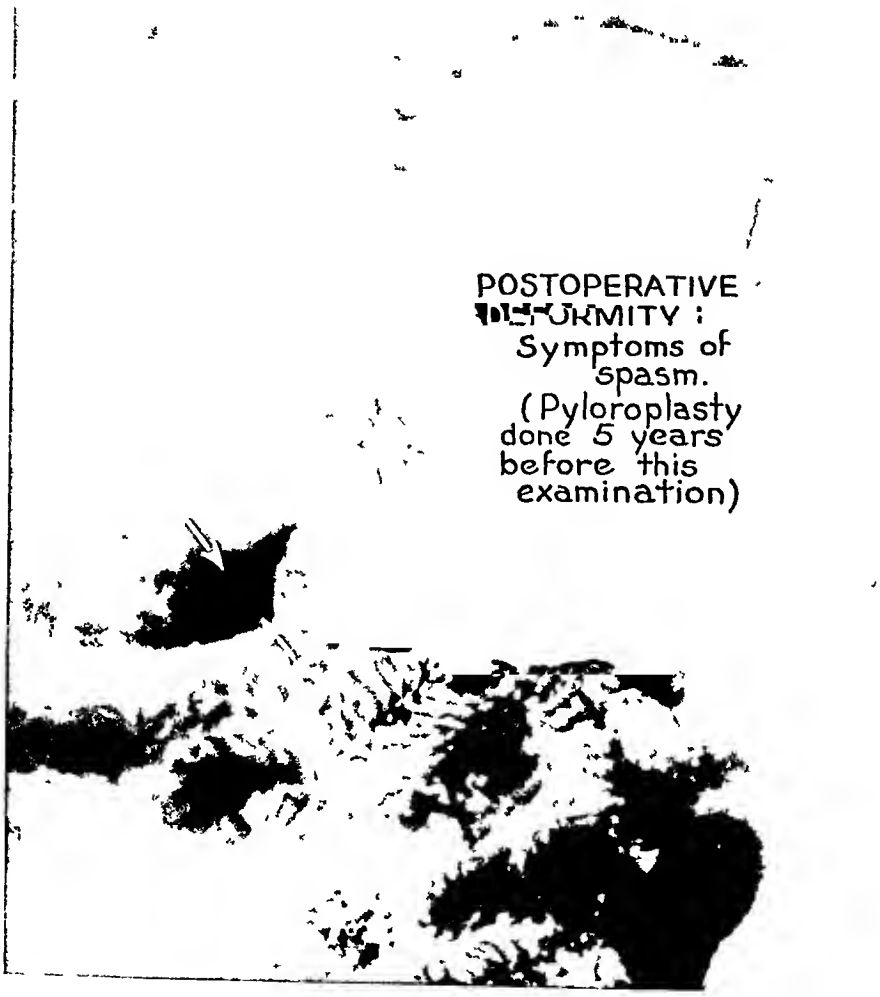

FIG 6 CASE 6

a negative finding should elate them, there have been a few patients who instead of being delighted that the finding was negative and appreciative of our desire to protect them against a possible early malignancy, have remained critical and of the opinion that with adequate investigation and study such a conclusion could have been reached without surgery. If every one of the patients whom we have explored for this finding had assumed this position,

I would still in the presence of such a persistent prepyloric defect advise exploration because that is what I would wish to have myself.

Another difficulty which presents itself to the gastric surgeon is prepyloric thickening with no evidence of tumor or ulcer. Here the decision is often difficult, trying and worrisome. In such a lesion the surgeon can rarely be aided by biopsy, and he is faced with the apprehension that if he does a subtotal gastrectomy, the pathologic report may show no evidence of ulcer or malignancy. He will then have exposed the patient to the hazard of an extensive operative procedure.

Three conditions have presented difficulty of decision concerning prepyloric thickening, at the operating table with the abdomen open and the prepyloric region exposed: (1) localized or segmental prepyloric gastritis, (2) a small ulcer within the pyloric sphincter where it cannot be palpated, with secondary induration about the prepyloric region, (3) lymphosarcoma infiltrating the wall, and (4) early intramural type of infiltrating carcinoma of the stomach called the linitis plastica type.

I do not believe that anyone can formulate a set of rules for these cases, since each is a problem in itself. We must admit to having resected stomachs with such lesions, uncertain as to what they were, and to having received pathologic reports postoperatively of all the conditions mentioned. One can only generalize, I believe, as to prepyloric thickening without diagnostic evidence of ulcer or tumor, to the effect that the decision must be made for or against immediate subtotal gastrectomy on the basis of the ease with which the stomach can be resected, the general condition of the patient and his ability to withstand the procedure, and the correlation of the patient's symptoms and findings.

Our difficulty in deciding whether subtotal gastrectomy should be done in these uncertain prepyloric thickenings has been very much simplified within the last few years. This is due to improved anesthesia and greater and now large experience with the operative procedures of subtotal and total gastrectomy. With these and improved postoperative management, the mortality of subtotal gastrectomy has now been reduced to a level where when in doubt we hesitate very much less to apply the operation in these uncertain cases than we did when the operative risks were greater. We have now done 230 consecutive subtotal gastrectomies for ulcer with a mortality rate of 2.7 per cent, and included in these 230 subtotal gastrectomies for ulcer were 45 gastrojejunal ulcers. In addition to these, we have had 7 gastrojejunocolic fistulas requiring not only resection of the stomach and jejunum but also the right colon and transverse colon.

We do not feel that even with this low mortality rate, total gastrectomy

should be employed on the basis of suspicion. Certainly, however, when one realizes the frequency with which malignancy does occur in the prepyloric region, that with thickening in the prepyloric region an ulcer can exist within the pyloric sphincter and still not be demonstrated by palpation, that localized gastritis is at least under very grave suspicion as a possible forerunner of carcinoma, and when combined with this the mortality rate of subtotal gastrectomy is now so low, our conscience troubles us but little if after subtotal gastrectomy for such an uncertain prepyloric thickening the pathologic report is gastritis. We feel, in addition, that the small number of patients in whom the early diagnosis of malignancy of the stomach is now being made, that the low operability rate which is constantly facing us in dealing with this lesion, and that the low five-year nonrecurrence rates after subtotal and total gastrectomy for malignancy of the stomach, constitute a far from satisfying state of affairs. In the presence, therefore, of even an uncertain lesion in this prepyloric region, where malignancy is so prevalent, an aggressive and radical approach is well justifiable when a consideration of the patient as a risk and our operative mortality figures support the indications for such decision.

THE KNOWN AND THE UNKNOWNS IN THE PROBLEM OF OPTIMUM NUTRITION

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Our knowledge of the composition of foods, the role of foods in the living body and the specific requirements for the main groups of foods in the living organism—the proteins, fats, starches, inorganic salts, and vitamins—has increased enormously in the last fifty years. This detailed knowledge has, however, not gotten down very effectively to the man in the street, the woman in the average home, or the people in the factory and on the farm. More recently, the startling character of these biologic and chemical discoveries in human nutrition has, to my way of thinking, led to much unfounded anxiety, fear, wishful thinking, and questionable commercial exploitation.

REQUIREMENTS OF PROTEIN

Whether or not we can maintain optimum health on 25 grams or on 125 grams of protein per day depends largely on the kind of proteins we eat, as the biologic or nutritional value of proteins differs greatly. Some ten so-called *essential* amino acids are now known. These protein "building stones" are so called, because the human body cannot make them from the other nitrogenous elements in the diet. However, these essential building stones are present in varying amounts in nearly all proteins of animal and vegetable origin. If man eats a sufficient variety of natural foods he will get all the essential aminocids needed for health. Meats, milk, eggs and grains provide good food proteins. The first principle in adequate dietary proteins is accordingly: *variety, natural foods, omnivorousness.*

ESSENTIAL FATTY ACIDS

Up until yesterday even experts in nutrition thought that the nutritive significance of the animal and vegetable fats in our dietary, besides providing flavor, was: (1) energy or calories, and (2) carriers of such dietary essentials as vitamins A, D, and possibly others. It now seems highly probable that two or three of the numerous fatty acids in the animal and vegetable fats are as necessary in our diet as are the essential amino acids of the proteins. But, as in the case of the proteins, nutritional welfare of man lies *in variety and omniverousness*, since these essential fatty acids occur widely in plant and animal fats.

As for the phospholipids of the vertebrate nervous system, the human fetus, like the fetus of other mammals, not to mention non-mammalian species,

gets them or makes them from food constituents other than the specific products of the mammary glands.

THE CARBOHYDRATES

Digestible carbohydrates occur usually in abundance in most of our natural foods. Dextrose, the sugar of the blood, is a necessary constituent for our internal environment. A large part of our heat and energy requirement can and should come from the starches. The starches are our most easily digested foods. So necessary is our blood sugar (dextrose) that, as in prolonged fasting, the body appears to manufacture it from body proteins, and possibly from the body fats. It now seems clear that our body can do the same with the proteins and the fats of our common foods. Hence no specific or distinct dietary deficiency disease is known as due to too little starch in the diet. A form of malnutrition, obesity, may be caused by eating too much starch, or sugars, as the carbohydrate in excess of our energy needs is readily converted to and stored as body fat. However, some of the important dietary deficiency diseases have come about, not by eating too much starch, but eating too little of the other important elements in the natural grains. I refer to the polishing of rice and the modern milling of wheat for white or patent flour, to the disease of beriberi and, to a more limited extent, anemia and rickets, and the vitamin A factor. The germ and the outer coats of the grain holds valuate proteins, vitamins, and minerals. Human dietary safety on this front would seem to be: go back to first principles, *putting the whole grain into the flour and the bread.* This can be done. We can learn to like it.

I believe we could learn to prevent the oxidative rancidity of whole grain flour. If we insist on milling the wheat and storing the flour, instead of storing the wheat, and milling as needed, there are now known relatively non-toxic antioxidants that might prevent the rancidity of whole grain flour that takes place on long storage. And until we have that problem licked, what is the matter with storing the wheat and milling the flour as we need it? I do not see any essential economic principle in storing the flour in place of storing the wheat. In my judgment, the recent addition of a little of the vitamins and minerals now milled out of the grain, and singing paeans of dietary salvation over this "enriched" flour and bread is not a sound policy either for today or tomorrow. Let us get back to first dietary principles on this front. The whole wheat, rye, or rice grain is one of our most valuable and our least expensive protective foods. On the whole we can trust nature further than the chemist and his synthetic vitamins. Recently Professor J. C. Drummond (1), the scientific advisor to the British Ministry of Food, voiced his reluctance to put the dietary safety of a nation on synthetic vitamins, as a long range policy. He thinks we must, and should, provide the natural vitamins in the

natural foods. I stand on that platform, until we know a great deal more than we know today about foods and human nutrition.

THE MINERALS OF OUR DIET

It appears true that for our forbears, except for the element iodine in restricted areas of the earth, the dietary need of minerals was efficiently met by the common non-purified, non-processed natural foods. So far as I know, this would still hold true, except for the cooking of such foods as meats, fruits and vegetables, and the habit of discarding the cooking water. To be sure the otherwise excellent natural food, milk, is so deficient in iron that an exclusive diet of milk for weeks or months brings on an anemia due to the iron deficiency in the diet.

How does the American dietary stand as to some of the essential mineral needs such as calcium, phosphorus, iron and iodine? The iodine deficiency in the states whose soil and water were depleted of iodine by the waters from ancient glaciers is now taken care of by putting the iodine back into our table salt. The iodine was there before our ingenious chemists learned to take it out. Insofar as purification deteriorates our foods, the science of chemistry does not serve man's welfare. Professor C. H. Sherman of Columbia University, an outstanding expert on nutrition, has long held the view that the American diet is probably too low in calcium, and possibly in phosphorus for optimum nutrition. This problem is complicated by the fact that a modicum of vitamin D is involved in the adequate absorption and utilization of calcium and phosphorus, particularly in the growth and maintenance of our bones. *I wonder if the possibility of a dietary danger in this field could not be met, universally and without cost, by adding a little calcium, phosphorus, and iron, to our table salt.* This should offer no insurmountable difficulties, and there is no evidence that a slight excess above actual needs of these minerals works any injury to our health.

We are urged to eat milk for its calcium. Yes, milk is a good source for lime. But milk is a relatively expensive food, and even in our country, with a plethora of foods, there is not enough milk to go around, at least as long as we insist on butter and cream for our tables, and turn so much of the valuable skim milk into channels other than human food. It is estimated that not less than 50 billion pounds of skim milk a year are diverted to other uses than food for man. We have federal and state laws restricting some uses of skim milk for human food. Such practices and laws are not in the interest of optimum national nutrition.

THE VITAMINS

How much of them do we need for optimum health? Where shall we secure them: in the drug store or the grocery store? That the disease *scurvy*, induced

by prolonged subsistence on dried, cured and cooked foods, can be cured by eating some fresh or raw fruits, vegetables, potatoes, leaves, or grasses has been known for more than a hundred years, but the specific chemical substance involved (ascorbic acid or vitamin C) is of very recent acquaintance, and the precise role of this vitamin in our cellular health is still largely unknown. *Pellagra* (vitamin B deficiency), *beriberi* (vitamin B deficiency) and *rickets* (a combination of vitamin D, calcium and phosphorus deficiency) are old human ailments, but their precise etiology and partial conquest belong to the last fifty years.

The recent advances in our knowledge of the chemical nature and the biologic role of the vitamins have been so rapid and so startling that, as usual, man's wishful thinking hopes to find in them the cure for nearly all the physical and mental ills to which the flesh is heir. In fact, the miracles now claimed by some misguided people for vitamin pills, natural and synthetic, rival the miracles of Lourdes. For instance, giving a mixture of table salt, vitamin C, and vitamin B_1 to workers in very hot environments, observing reduction in fatigue and heat prostrations, and concluding that the vitamins contribute to this desirable result is not scientific (8). For we know that under such conditions NaCl alone produces these results, and it is difficult to measure fatigue with accuracy. Vitamin concentrates are useful aids in the hands of a physician. The tragedy and waste in the 1942 vitamin pill business is this: *most of the people who can afford to buy them do not need them; most of the people who may need them cannot afford to buy them.*

Under the heading, *Vitamins and the Future,* the chemist R. J. Williams (2) presents the following extraordinary assertions and generalizations: "It is recognized already that one vitamin can and does cure mental derangements." This is stated without qualification, while as a matter of fact mental derangements are due to a great diversity of factors, including heredity, mechanical and chemical trauma, and cerebral ischemia. The value of the vitamin B complex in mental derangements seems to be limited to those accompanying advanced pellagra and chronic alcoholism. Dr. Williams goes on to say: "Good diets, which mean an abundant supply of vitamins, promote intellectual keenness. . . There can be no doubt that much dullness on the part of school children . . . can be traced in part to lack of the proper kind of food and especially lack of enough vitamins." These are broad and important generalizations. But I know of no evidence that an ample ingestion of vitamin pills will materially improve the scholastic record of the millions of children and young adults in our schools. Dr. Williams' assertions are just too good to be true. Human biology is not that simple. In his final seven-league stride Dr. Williams assures us that "intelligence and morality go together. . . . Since an ample supply of vitamins can foster a high intelligence, it has also the capability of fostering morality!" If this be true, and if we further admit that lying and injustice are phases of immorality, the

vitamin deficiency in the human race of our generation is indeed appalling! This chemist appears to know a lot about the causes of human disease, and some of the requisites for optimum physical health, optimum mental performance and social behavior of man that even the best of biologists and physicians have not yet discovered. When we have the vitamins that prevent dishonesty and injustice, the millenium will have come. But as I read and listen to the modern propaganda for vitamin pills, I am led to suspect that at least some vitamin vendors do not take their own medicine. They just sell it.

In an earlier paper another chemist, Dr. R. R. Williams (3) suggests that a liberal intake of vitamins has made the Germans pugnacious and bellicose. "They (the Germans) have enjoyed a more generous supply of thiamin and other vitamins which grains provide than have Scandinavia, the Low Countries, France, Spain, Italy, or the British Isles. Perhaps pacifism is a product of malnutrition." If we scramble the biologic dicta of these two chemists (J. R. Williams and R. R. Williams) we seem to arrive at the remarkable conclusion that war, more war, is the optimum ethical activity of man, due to optimum vitamin ingestion, for is it not claimed that an abundance of vitamins in our food makes us more intelligent, more moral, and more bellicose? What next?

Fortunately *all of the known vitamins (except thiamin and vitamin C) are relatively stable* so that the common methods of preserving, sterilization, and cooking of foods do not destroy or eliminate them completely. And they are widely distributed in nearly all of our natural foods. But they can be eliminated by such modern food processing as milling of grains, polishing of rice, and hydrogenation or chemical hardening of plant or animal fats. The precise quantities of each of these vitamins needed by man for good health is not known. The quantity needed can apparently be secured by eating enough of natural foods, including some raw fruits and vegetables. All of the vitamins are stored to certain extent in the body organs of man and animals, so that a fast of a month or more does not bring on any vitamin deficiency detectable by our present tests. This is to say, in time of plenty we store against a season of scarcity, so that without fresh fruits or a vitamin pill for breakfast we do not have scurvy, rickets, beriberi, or psychosis by noon of the same day, or even the following month.

The *wide distribution of the known vitamins* in natural, non-processed foods both of animal and vegetable origin, is indicated by the facts that meats (including fish), eggs, milk, whole grain, fruits, legumes, and vegetables are all good sources of the known vitamins. Citrus fruits carry an abundance of vitamin C, but if these are not available, or too high priced for the consumer's pocket book, the lettuce, the carrot, the cabbage, or the tomato yield us all we require. The known and serious vitamin deficiency diseases came about by too much refining, processing, and cooking of foods, and by diets

too limited in variety. Again, *we see dietary health insurance in the eating of the greatest variety of natural foods, for in no other way did our ancestors, or the wild animals of the jungle and the plains, survive and prosper.*

WHAT ARE THE MECHANISMS OF THESE NATURAL DRIVES OR URGES OF HUNGER AND APPETITE?

We know today very much less about the precise mechanisms of appetite for food than we know about the mechanism of hunger, but stated briefly, appetite for food in contrast to hunger does not seem to be primarily inherited. It seems to be a memory of previous pleasant experiences with foods, pleasant experiences in the sense of taste, odor and visual appearance of foods.

One fact stands out clearly in the matter of appetite, and that is this: *All normal people seems to be able to acquire a liking or appetite for any kind of substance that can serve the nutrition of man.* This, I think, is a factor of safety as well as a factor of danger in human diet. The factor of safety appears in the human capacity for omnivorousness, that is, consumption of a great variety of foods. There is no doubt that this tendency or habit of omnivorousness will in part explain the dietary success of our forbears, and of wild animals, in the absence of specific understanding of food requirements. On the other hand, there is danger in combining the products of human ingenuity in the matter of food processing and food preparation with the capacity to develop liking for foods that are so defective in essential elements that when they are made a preponderant part of our diet, we may develop serious malnutrition. Three of such common foods today are the refined sugars, polished rice, and bread made out of our modern patent flour. These are good foods. We can, and we have developed appetite for them, but because of refinement, they are so defective in many essential dietary elements, that they can lead, in fact they have led, to nutritional disaster when they make up too large an element in our over-all food consumption. I think it is particularly important to recognize the safety in dietary omnivorousness, to recognize the fact that we can and should develop liking for, that is appetite for, a great variety of foods as soon as feeding at the breast or by bottle is supplemented by the common foods of man, because these likings or appetites are probably most easily established in the early years of life. They can, however, be developed after maturity.

HOW BAD IS THE AMERICAN DIET?

We have heard in the last eight years from many sources that a third of our population, or roughly 40 million citizens, are underfed, in addition to being poorly clothed and poorly housed. Now that has been added to recently, so that today not 40 million, but 95 million Americans either cannot get the

right food, or have such bad habits that they don't eat enough of the right food. If this is so, we have before us a tremendous problem of malnutrition in our once happy land! How bad is the American diet today?

In the National Geographic Magazine of March, 1942, Mr. J. R. Hilderbrand asserts that our "machine food age—born of roads, research and refrigeration—has made the United States the best-fed nation in history." Is this sweeping assertion based on biologic and medical evidence of yesterday and today? It appears to be an inference from the wealth and variety of our food resources.

According to Dr. Rowntree (4) the first two million men, age 21 to 35, examined in the 1942 U. S. Army draft had an average height of 67.5 inches, or exactly the same average height as our drafted men in World War I. But the 1941 men were on the average 8 pounds heavier than the Army men of 1917–'18. We do not know whether these 8 pounds represent muscle, bone or fat. But these data on the 1941 draftees do not support the assertion of Surgeon General, Dr. Thomas Parran, that less than 25 per cent of our population now has an adequate diet. According to the *Statistical Bulletin* of the Metropolitan Life Insurance Company the mortality statistics of this company's 1941 policy holders showed an average life span or life expectancy of 63.42 years, an all-time high for our country. Mortality statistics reflect many important factors, besides the human diet. But so far as such statistics go, they give no support for the claim that one hundred million Americans are malnourished.

The assertions of Dr. Thomas Parran appear to be based primarily upon a series of surveys conducted by the Bureau of Home Economics of our Federal Department of Agriculture, assisted in some of the field work and statistical analysis by the Department of Labor. These surveys embraced some 4,000 urban and village families of various levels of income and some 2,000 rural families of varying levels of income, selected from representative regions of our country. The surveys consisted in reports from these families as to how much money they spent for food, and what kinds of food were bought, and, in the case of rural families, how much and what kind of food they consumed from the crops on their own farms. Remember these field investigators (some of them on WPA) had to take or did take the people's word for all of these alleged facts. It is impossible to evaluate or determine the degree of accuracy or honesty (accuracy as to memory) of whatever member of these families gave the facts or alleged facts to these enumerators. All physicians with some experience know how difficult it is to secure reliable information on food consumption from an individual, even for a much shorter period than a year. And the members of these 6,000 families were not subjected to medical examinations.

Sometime ago (5), I asked Surgeon General Parran for better evidence that our national dietary is tragically defective, is so bad as to be called U. S. Problem No. I, even in the face of our all-out war. To my knowledge this evidence has not yet appeared, unless the report by Doctors Jolliffe, McLester and Sherman (6) on "The Prevalence of Malnutrition" may be so construed. These authors endeavor to answer the question by the following approaches:

(1) The Bureau of Home Economics Surveys of kinds and quantities of foods purchased in a very small sample of our population.

(2) Mortality statistics (pellagra, beriberi, scurvy, rickets) for 1933–'38. Deaths from pellagra are recorded as around 3,500 per year for 1933–'38. This does not speak well for education, our food habits, or our national ingenuity, since it can be prevented by a cake or two of yeast a day. We do not seem to have made much of an inroad on pellagra since the classic studies of Dr. Goldberger. It seems the people concerned will not eat yeast, even when supplied free. If natural foods containing sufficient niacin cannot be supplied, or will not be eaten in sufficient quantity, it would seem a part of wisdom to add niacin to one of the common food staples in the states where pellagra prevails, for this dietary deficiency disease appears to be our largest problem, at present.

Deaths from rickets run from 250 to 350 per year. Of course, this is no indication of the prevalence of rickets among our children, for rickets is a debilitating, not a killing disease. Deaths from scurvy in our country during these three years are almost non-existent (about 30 per year). There appears to be a slight increase in the deaths from beriberi, but these deaths are so few as to be almost negligible.

We are, of course, well aware of the uncertainties in all mortality statistics. Except for pellagra, where the estimates run as high as 100,000 patients annually, the other mortality statistics do not give support to the assertion that from one-third to three-fourths of our population is subsisting on an inadequate diet.

(3) The evidence of malnutrition from the records of United States hospital admissions does not argue for wide-spread food deficiency disease in our country, even when we admit that most if not all incipient malnutrition escapes recognition. In the case of vitamin deficiencies, the average admission from five large general hospitals, in different parts of our country ran only 0.14 per cent. Deficiency in the intake of iron is usually a minor factor in the hospital records of anemia. And it does not seem fair to class alcoholic neuritis with the dietary deficiency diseases, for here the primary factor is a degree of chronic alcoholism which prevents sufficient ingestion of available foods.

While I agree in the main with the final conclusion of these authors: "Some types of malnutrition are strikingly obvious to every person, some are apparent only to the physician who looks for them, and some are vague and elusive even to the careful observer. . . . The evidence at our disposal warrants the conclusion that dietary inadequacies and malnutrition of varying degrees are of frequent occurrence in the United States, and that the nutritional status of an appreciable part of our population can be distinctly improved," I fail to find even in this report any basis for the assertion that 100,000,000 fellow citizens are below par through the diet. "Frequent" and "appreciable" are not quantitative findings.

In the Journal of the American Medical Association (7), a subcommittee on Medical Nutrition of the National Research Council presents a report on malnutrition, under the following heading and with the following tables of signs and symptoms:

RECOGNITION OF EARLY NUTRITIONAL FAILURE IN INFANTS, CHILDREN, ADOLESCENTS AND ADULTS*

Tentative clinical criteria for physicians: Complete list of symptoms and signs classified according to persons capable of observing them

Symptoms and signs suggestive of early deficiency states in infants and children

Symptoms		*Physical signs*	
1. Lack of appetite	(L)	1. Lack of subcutaneous fat	(N)
2. Failure to eat adequate breakfast	(L)	2. Wrinkling of skin on light stroking	(N)
3. Failure to gain steadily in weight	(L)	3. Poor muscle tone	(D)
4 Late period of sitting, standing, walking . .	(N)	4 Pallor	(N)
5. Aversion to normal play	(N)	5. Rough skin (Toad skin)	(N)
6 Chronic diarrhea	(L)	6 Hemorrhage of new born (k)	(D)
7. Inability to sit	(L)	7. Bad posture	(L)
8. Pain on sitting and standing	(L)	8 Nasal blackheads and whiteheads	(N)
9 Poor sleeping habits	(L)	9 Sores at angles of mouth, Cheilosis	(L)
10 Backwardness in school	(L)	10 Rapid heart	(N)
11. Repeated respiratory infections	(L)	11 Red tongue	(D)
12 Abnormal intolerance of light, photophobia	(L)	12. Square head, wrists enlarged, rib beading	(N)
13. Abnormal discharge of tears	(L)	13. Vincent's angina, thrush	(D)
		14 Serious dental abnormalities	(N)
		15. Corneal and conjunctival changes—slit lamp	(D)

L, those which parents or teachers might observe.

N, those which nutritionists or nurses might observe.

D, those which physicians only would be expected to observe The physician would take into account all other symptoms whether or not they have been previously observed.

Symptoms and signs suggestive of early deficiency states in adolescents and adults

Symptoms			
1. Lack of appetite	(L)	5 Red swollen lingual papillas	(D)
2 Lassitude and chronic fatigue	(L)	6 Glossitis	(D)
3. Loss of weight	(L)	7. Papillary atrophy of tongue . .	(D)
4. Lack of mental application	(L)	8 Stomatitis	(D)
5. Loss of strength	(L)	9 Spongy, bleeding gums	(L)
6 History of sore mouth or tongue	(L)	10 Muscle tenderness, extremities	(D)
7. Chronic diarrhea	(L)	11. Poor muscle tone	(D)
8 Nervousness and irritability	(L)	12 Loss of vibratory sensation	(D)
9. Burning, prickling of skin, paresthesias	(L)	13 Increase or decrease of tendon reflexes	(D)
10. Night blindness	(N)	14 Hyperesthesia of skin	(D)
11. Abnormal intolerance of light, photophobia	(L)	15. Bilateral symmetrical dermatitis	(D)
12. Burning or itching eyes	(L)	16 Purpura	(D)
13 Abnormal discharge of tears, lacrimation	(L)	17. Dermatitis, facial butterfly casal necklace, perineal, scrotal, vulval	(D)
14 Muscle and joint pains, muscle cramps	(L)	18 Thickening and pigmentation of skin over bony prominences	(D)
15. Sore bleeding gums	(L)	19 Nonspecific vaginitis	(D)
16. Tendency to bleed	(N)	20. Follicular hyperkeratosis of extensor surfaces of extremities	(D)
Physical signs		21. Rachitic chest deformity	(D)
1. Nasolabial sebaceous plugs	(N)	22. Anemia not responding to iron	(D)
2. Sores at corners of mouth, cheilosis	(L)	23. Fatigue of accommodation	(D)
3 Vincent's angina	(D)	24. Vascularization of cornea	(D)
4 Minimal changes in tongue color or texture	(D)	25. Conjunctival changes	(D)

I fully agree with this Committee when it says: "... there is imperative need for (a) determination of the actual incidence of early deficiencies among the general population and for (b) the establishment of satisfactory diagnostic criteria for the recognition of such conditions." But after tabulating no less than 29 alleged signs and symptoms of early or incipient dietary deficiencies *that even laymen might observe and diagnose,* the Committee seems to wipe out its entire tabulation and report by this statement: *"Implicit in the definition of the problem and in the foregoing statements is the fact that no symptoms or physical signs can be accepted as diagnostic of early nutritional failure.* Certain symptoms and physical signs, however, when verified by a competent physician and when other possible causes have been ruled out, should be considered as significant indications." If this latter statement is true, and I subscribe to it, the above tabulation is misleading, if not false in toto, insofar as present known facts of incipient dietary deficiencies are concerned.

EDUCATION

If a third to three-fourths of our fellow citizens are as ignorant about foods as (and have no better eating habits than) the people in the middle and higher income brackets, it is clear that we will not materially improve the American dietary by providing the alleged underfed forty million Americans with more cash, even assuming that we could "freeze" food prices. For cash or no cash, too many people will fail to grow, or purchase, and consume the requisite ingredients of an adequate diet. *I see no escape from the long and stony road of education.* I am telling you nothing new when I say that there is a crying need for more and better teaching of what is now known about foods and human nutrition, from the kindergarten to the university. The synthetic vitamin automatically providing this better teaching is not yet discovered. I wonder if a thorough understanding of the machinery of the human body and what it takes to run this machinery with efficiency, and free from avoidable tragedies, is not as important as familiarity with our country's history, our poets, and our heroes of peace and war. Such understanding seems more important for the good life in our land than proficiency in Latin grammar, and the speaking acquaintance with the poetry of Homer, the philosophy of Plato, and the tragedies of Shakespeare. Our fellow citizens are all wrong when they assume that such understanding is necessary, appropriate and significant only for the physicians. And physicians should never forget that a doctor is more than a healer, he is also a teacher; a teacher who, on this topic, could and should reach both the child and the parents, without the delays and dilemmas encountered in Boards of Education, school budgets, and theories of education among educators.

CONCLUSIONS

1. Many human ailments, such as chronic infections, worry, etc., not yet known to be caused by faulty diets, do interfere both with the ingestion, digestion, and the utilization of adequate kinds and quantities of foods needed for man's optimum health. Such diseases may lead to varying degrees of malnutrition, quite apart from ignorance, poverty, faulty dietary habits, or food scarcity. Even laymen can see that good foods are not a cure-all for such health impairments.

2. In addition to these diseases of non-dietary origin, there is in our country today some impairment of health primarily due to defective diets, health impairments clearly recognizable as due to defective diets, health impairments clearly recognizable as due to defective diets by present medical, chemical and biological criteria. But we do not know the extent of this malnutrition in our population, nor what percentage of it is due to ignorance, to faulty food habits, or to poverty. *We do know that it is not due to food scarcity.* That being the case, this malnutrition could be wiped out.

3. Since man and his health constitute our most important natural resource, we should proceed without delay and with all the brains at our command to find better and more reliable methods to diagnose the signs and symptoms of *incipient dietary deficiencies.* Such knowledge will give us a clearer understanding of what constitutes an optimum diet for optimum health, so far as health is determined by diet alone. This, it seems to me, is a primary charge on the science of medicine, the science of biology, the science of chemistry. But we who labor in these fields will proceed faster along these lines, if we are encouraged by an understanding of the urgency and the difficulties in the problem and the cash cost of its solution on the part of all citizens.

4. Pending this greater scientific understanding as to human food needs for optimum health, these important things can and should be done now: (*a*) cleanse our present food and nutrition education of all fads, of all selfish commercial and hyopic political propaganda. In the field of human nutrition the method of science is the only path forward. And, (*b*) move our nutrition education from the ivory tower down to the comprehension and appreciation of the common man. We have the brains and the cash to do both. Have we the will to carry on this difficult task, when a possible better national health is the only goal, the only reward? I wonder.

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CORRELATION OF CYTOLOGICAL WITH CHEMICAL CHANGES IN THE LIVER AS INFLUENCED BY DIET, PARTICULARLY PROTEIN

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Few attempts have been made to correlate histological changes in the liver with its chemical composition of protein, particularly as affected by alterations in dietary intake. The influence of glucose ingestion on the glycogen content of the liver has been studied widely ever since the early observations of Claude Bernard. The fat content of the liver has more recently received much attention. While morphological changes can be demonstrated with varying content of glycogen and fat, there is a general feeling that even here the correlation is not exact and that chemical analyses offer a far more accurate picture of variations in fat and glycogen content than histological study even with special stains.

Two years ago in a paper from this institution (1) definite histological changes in the liver were correlated with a fall in the protein content of the livers of dogs made hypoproteinemic by a protein-deficient diet. In the present communication, additional evidence is examined which tends to establish more definitely a correlation between cytological changes and chemical content not only of protein but also of glycogen.

PREVIOUS WORK

Numerous studies on the influence of dietary protein on the liver have appeared, but the histological observations and the chemical determinations were each made by separate groups of observers.

Anatomical enlargement of the liver following a high protein diet is an old observation (2). Histological studies were made in 1914 by means of a special pyronin stain by Berg (3), who reported droplets in the liver which he believed represented storage of protein inasmuch as they were present in well fed animals and disappeared during fasting, yet reappeared with protein ingestion but not with carbohydrate. Li (4) in 1936, using a similar technique, confirmed Berg's observations and also noted that bleeding among other things caused disappearance of the droplets. The most complete histological study of the liver as influenced by the ingestion of various diets was reported by Noel (5) in 1932, who noted among other things that the hepatic cell was largest following high-protein feeding.

In chemical studies, many observations may be cited both of the total

nitrogen content of the liver as well as actual determinations of several protein fractions isolated by various methods of extraction. The earlier literature was reviewed by Bleyer and Berger (6) in 1924. Luck (7) found increases in all of four protein fractions in the liver following a change from a low to a high protein diet. Not only was the liver larger on the high protein diet, but the protein content increased per gram of liver. Addis Poo and Lew (8) found a rapid fall in the total protein content of the liver, following a fast, which in one week reached a value of 40 per cent. A stimulating discussion of the subject of liver proteins by Luck (2) appeared in 1938.

METHODS

The liver samples were biopsies obtained from dogs under nembutal anesthesia; about 5 grams were used. The chemical procedures used in the determination of the fat, glycogen, and nitrogen content of the liver were described in a previous paper (1). The validity of using nitrogen content as a measure of protein concentration and the influence of perfusion on such determinations has been discussed elsewhere (1, 6, 7). For the present purposes relative changes are more significant than absolute values. It is of interest to note that the total nitrogen (s.t.6.25) of the liver in the normal dogs reported here, while somewhat high, agrees rather well with the values for protein obtained by others.

Sections of the same specimens used for chemical analysis were made after fixation in 10 per cent formalin; hematoxylin and eosin were used for the staining of sections after embedding in paraffin. Frozen sections of formalin fixed blocks were stained with Sharlach R. to demonstrate fat, and other sections of blocks fixed in absolute alcohol were stained with Best's Carmine to demonstrate glycogen.

In addition to what has been considered a normal kennel ration of lean meat and Purina chow, three types of diets were used in the present experiments on dogs. A *high protein diet* consisted of the ad lib administration of cooked lean horse meat. A *non-protein diet* was composed of a sucrose solution containing adequate electrolytes and Vitamin B (Labco). This non-protein diet was given by gavage twice a day; the energy value being 50 calories per kilogram per day. A *fast* implied absence of all food, although water was allowed ad lib. The diets used in the experiments on rats are described in table 2.

EXPERIMENTAL OBSERVATIONS

In all, study was made on the livers of 25 dogs and a number of rats, fasted as well as fed on diets varying in protein and carbohydrate content.

The observations and their correlations can be illustrated by a few repre-

sentative examples of the findings in dogs and by a table describing a series of experiments in rats (table 2).

Following are descriptions of the observations made on individual dogs:

1. *Normal control.* A healthy dog, Z-22, weighing 5.8 kilograms, had been fed the regular kennel ration. The absence of protein depletion was indicated by the fact that both the serum protein and the concentration of the liver nitrogen determined on a liver biopsy were normal; the concentration of liver glycogen was also within normal limits (table 1).

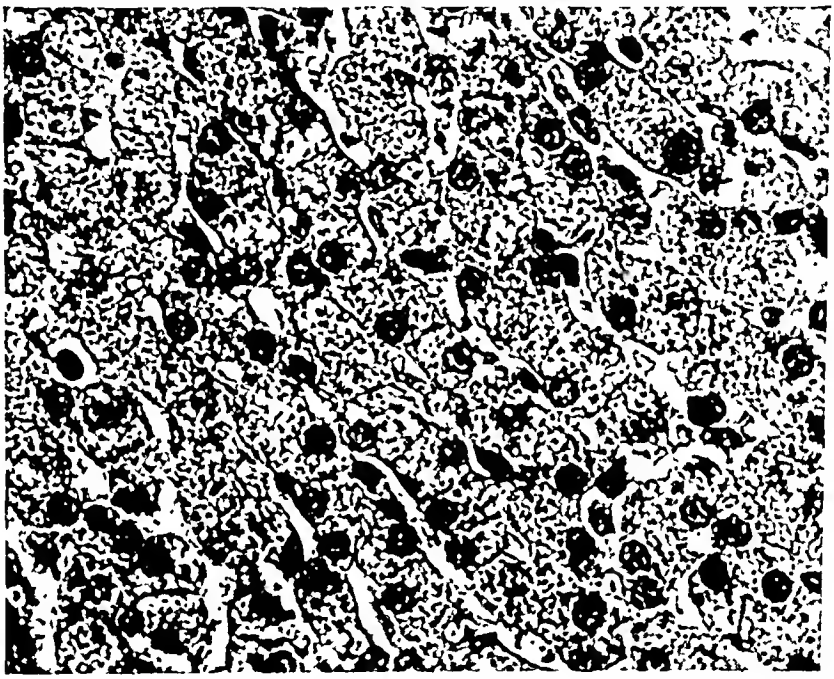

FIG. 1. (570×) Normal control. A section of liver of a dog (Z-22) fed a diet adequate in protein. Note that the size of the cells and the density of the granular cytoplasm are intermediate between those shown in figure 2 and figure 3. The concentration of both nitrogen and glycogen was normal.

A histological section of a liver biopsy (fig. 1), stained with hematoxylin and eosin, shows an essentially normal picture. The liver sinusoids stand out clearly but are not exceptionally wide. The cytoplasm of the liver cells has abundant rounded or irregular eosinophilic granules which are only slightly separated from each other. There are a few distinctly outlined small round vacuoles, such as may be seen in cytoplasm containing stainable fat. The nuclei are uniform in size. They contain one distinct nucleolus, or occasionally two, and evenly dispersed, finely granular chromatin. Following the first biopsy this dog was fed a high protein diet for one week. At the end of this period a second biopsy showed the same chemical and histological features as in the biopsy taken before the administration of the diet rich in protein.

2. *Effect of non-protein diet.* A dog, E-20, weighing 5.3 kilograms when killed, had been fed the low protein diet for three weeks. Both the liver nitrogen concentration and the total liver nitrogen, calculated as a percentage of body weight (table 1), were extremely low; the liver glycogen concentration extremely high. A section of the liver of this animal (fig. 2) shows narrow sinusoids which appear to be compressed by wide cords of liver cells. The individual liver cells are large. The cytoplasm contains little stainable material so that it appears rarified. There are only a few eosinophilic granules or strands in an otherwise unstained cytoplasm. The cell membranes are sharply

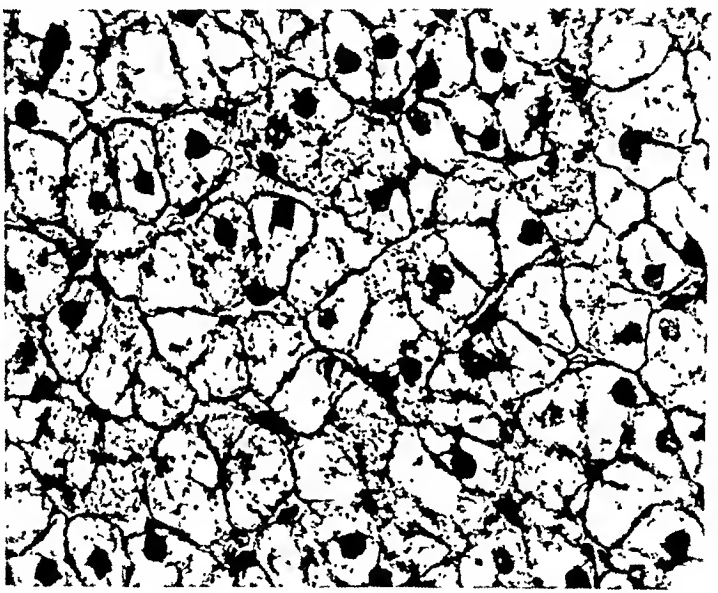

FIG. 2. (570×) Section of liver of a dog (E-20) fed the non-protein diet. Note the large cells, rarified cytoplasm containing little stained material and inconspicuous sinusoids. The concentration of nitrogen was low, of glycogen high.

stained. There are no distinct round vacuoles. At times the eosinophilic strands within the cytoplasm appear to extend from the nucleus to the cell membrane. The appearance of these liver cells is that frequently referred to as hydropic degeneration. In general, the nucleus occupies a central position and is never flattened or displaced to one side of the cell. The nuclei are of uniform size and show approximately the same amount and distribution of chromatin as those in the liver cells of Z-22, the control animal which had received an adequate diet.

3. *The effect of a fast.* Dog 68N had been fed the non-protein diet for 3 weeks as in the previous experiment (dog E-20), but was fasted for 54 hours

before it was killed. Chemical studies of this liver (table 1) demonstrated a normal liver nitrogen concentration, but the total liver nitrogen, calculated as a per cent of body weight, was low. The liver glycogen concentration was extremely low. In the sections of this liver (fig. 3) the sinusoids, clearly seen with the low power of the microscope, are obviously wider than those observed in the normal control (fig. 1). The cords of liver cells are narrow, frequently not more than twice the width of the average sinusoids. The individual liver cells are small. The cytoplasm is smaller in amount than that of liver cells

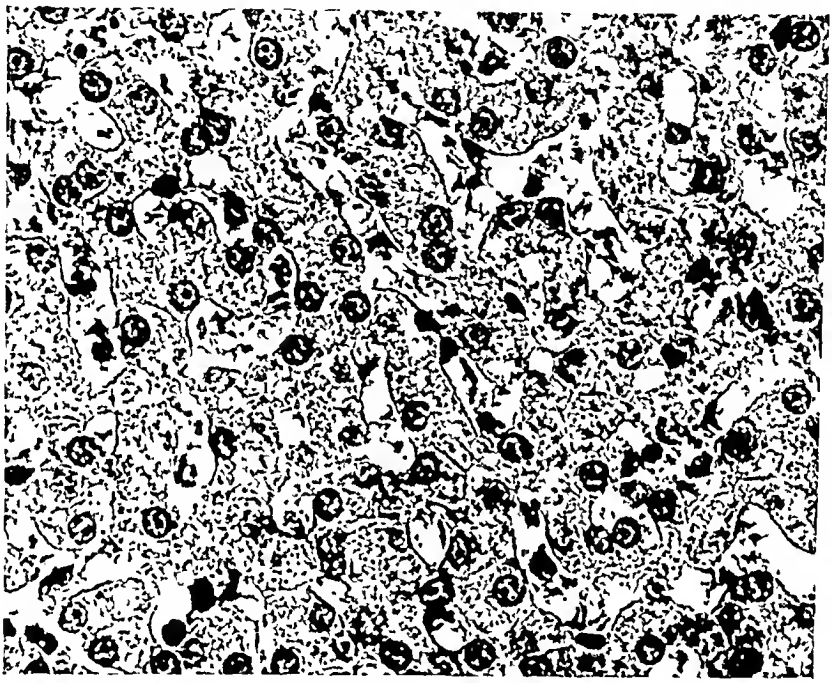

FIG. 3. (570×) Section of liver of dog (68N) fed the non-protein diet, then starved for 54 hours Note the small cells, dense cytoplasm, narrow liver cords, and wide sinusoids. The concentration of nitrogen was normal, of glycogen low.

of animals fed an adequate diet, but even more conspicuous is the change in its density. The eosinophilic cytoplasmic granules lie close together with practically no intervening clear zones giving the cytoplasm this dense appearance. The nuclei are fairly uniform in size and staining, but an occasional one is about $1\frac{1}{2}$ times as large as the average. The finely granular chromatin material of the nuclei is not uniformly distributed so that clear spaces occasionally appear in the nuclei.

4. *The effect of high protein diet.* Although dog 56 was a stock animal which had been fed for a short time on the regular kennel ration, chemical studies of the blood and of a liver biopsy indicated that the protein intake had probably been inadequate, inasmuch as the total liver nitrogen concentration was low

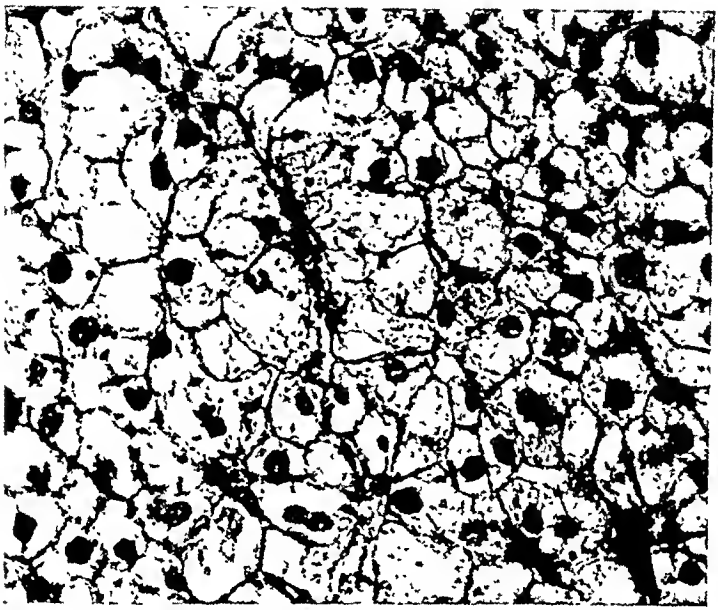

FIG. 4. (570×) Section of liver of dog (56) suffering a moderate protein depletion. Note that the section shows large cells with rarified cytoplasm from the periphery of a lobule. The narrow sinusoids are difficult to see. The concentration of nitrogen was low, of glycogen normal.

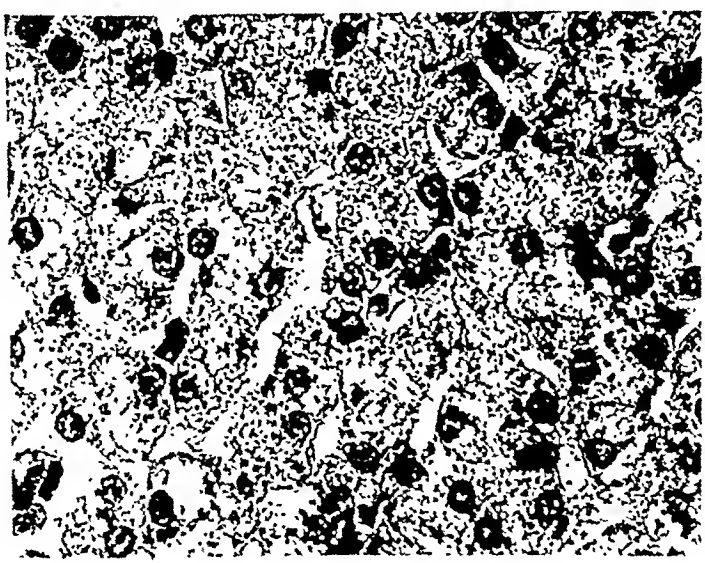

FIG. 5. (570×) Section of liver of same dog (56) as shown in figure 4, after one week on a high protein diet. Note the disappearance of the rarified character of the cytoplasm and an increase in the width of sinusoids. The concentration of nitrogen became normal.

TABLE 1

Summary of observations on dogs

	NORMAL CONTROL	NON-PROTEIN DIET	FASTING	MODERATE DEPLETION	HIGH PROTEIN DIET
Dog	Z-22	E-20	68N	56	56
Serum albumin (grams %)	4.14			3.28	3.94
Hematocrit (%)	50.9			42.3	37.7
Liver nitrogen (grams %)	3.25	1.31	2.95	2.39	3.03
Weight of liver (grams)		277	236		
Body weight (kilo.)		5.3	8.6		
Total liver nitrogen (as grams % of body weight)		0.068	0.081		
Liver glycogen (grams %)	3.1	17.8	0.05	7.6	2.7
Total liver glycogen (grams)		49.3	0.13		
Histological appearance of liver	Medium sized cells; cytoplasm moderately dense	Rarified cytoplasm; large cells	Dense cytoplasm; small cells; wide sinusoids	Rarified cells esp. at periphery of lobule	Same as normal control
See figure	1	2	3	4	5

TABLE 2

Summary of observations on rats after 2 weeks on experimental diet

RAT	DIET	BODY WEIGHT		WEIGHT OF LIVER	LIVER NITROGEN	TOTAL LIVER NITROGEN	HISTOLOGICAL APPEARANCE OF LIVER
		Before	After				
		grams	*grams*	*grams*	*grams %*	*grams*	
1	Basic*	220	164	6.5	2.38	0.154	Large cells rarified cytoplasm
2	Fast†	210	140	3.5	3 24	0 113	Small cells dense cytoplasm
3	10% Amigen‡	270	242	7.5	3 18	0.235	Moderate sized cells slightly rarified cytoplasm
4	20% Amigen	226	242	9.0	2.86	0.257	Moderate sized cells and moderate density of cytoplasm
5	30% Amigen	212	218	8.0	3.25	0 259	Moderate sized cells moderate density of cytoplasm

* Basic diet contained all dietary elements but no protein (except for that in vitamin supplement).

† Animal died on 13th day of fast.

‡ Amigen (an enzymotic hydrolysate of casein and pancreas) added to basic diet.

and the serum albumin below normal (table 1). After one week on a high protein diet the chemical analysis of another biopsy of the liver showed a normal liver nitrogen concentration and the blood a normal serum albumin.

A histological examination of the first biopsy of the liver showed some variation in the character of the liver cells, although many of them were large and had a rarified cytoplasm such as that already described for the animal on a low protein diet. The cells in the peripheral zones of the lobules making up approximately half of each lobule have only a few stained granules or irregular strands in an otherwise unstained cytoplasm (fig. 4). The cells in the center of each lobule have a more compactly arranged granular cytoplasm approaching the appearance of the liver cells of adequately fed animals. In the central part of the lobules the sinusoids are wider and the liver cells are slightly smaller than in the periphery of the lobules.

In the second biopsy, taken after one week of the high protein diet, the cells are more uniform in character than those of the biopsy taken one week earlier. All the cells (fig. 5) resemble closely those seen in control animals fed an adequate diet (fig. 1). The cells at the periphery of the lobules no longer have a rarified cytoplasm such as that present in the biopsy taken one week before.

SECTIONS STAINED FOR GLYCOGEN

As might be anticipated in sections of material fixed in absolute alcohol, considerable amounts of glycogen could be stained, both in the rarified cytoplasm of liver cells of the animals fed a low protein diet and in the liver cells of animals fed an adequate diet. However, the staining method (Best's carmine) did not demonstrate accurately the quantitative variations as determined by chemical analysis. Little or no glycogen could be demonstrated in the liver cells of the fasted animals.

FAT CONTENT OF LIVER AND SECTIONS STAINED FOR FAT

The amount of liver fat determined chemically was not significantly different in any of these animals and the fat demonstrated in histological sections showed no marked variations.

The results of other experiments with dogs as well as with a large number of rats were entirely comparable to those which have been described above in detail. In table 2 are recorded some of the observations made in rats. They show the correlation between the percentage of nitrogen in the diet, the liver nitrogen of the animal, and the histological character of the liver cells as seen in sections stained with hematoxylin and eosin. Glycogen determinations were not made on the livers of this group of rats.

SUMMARY AND DISCUSSION

The present observations show how profoundly the diet influences both the histological appearance of the liver as well as its chemical composition of protein and glycogen. Although observations were made of the fat content

as well as the microscopic appearance of fat with special stains, no significant variations were noted in any of the livers studied. Of additional interest was the fact that the quantitative variations in the amount of glycogen present could not be accurately determined from sections stained with Best's carmine.

The correlations observed can be summarized briefly as follows:

In the livers of dogs on the non-protein diet which contained adequate carbohydrate, chemical analysis revealed large concentrations of glycogen which were associated with a characteristic appearance of the cytoplasm. This cytoplasm appeared rarified, containing almost no stained material. The nitrogen concentration and total content of nitrogen was low and the blood showed severe hypoalbuminemia. However, the influence of a fast was such as to change the histological picture completely, the cells assuming a superficially normal character while the nitrogen concentration of the liver became normal. However, the total nitrogen of the liver as a percentage of body weight was low, and detailed histological studies showed that the cells were small with a dense granular cytoplasm and the nuclei close together. The glycogen content was, of course, extremely low.

In a normal appearing but protein depleted dog (as shown by hypoalbuminemia) the liver showed some rarefaction of the cytoplasm which was associated with a moderate content of glycogen. After a week of the high protein diet the rarefaction of the cytoplasm disappeared and this change was associated with an increase in the protein concentration of the liver whereas the glycogen concentration showed no conspicuous alteration. During this period of high protein feeding the hypoalbuminemia returned to normal.

In a series of rats smilar changes were observed. On a non-protein intake containing all of the other dietary essentials the size of the livers remained unchanged, but the cellular cytoplasm became rarified, the nitrogen concentration and the total nitrogen content became low. On a fast the liver became small and the nitrogen concentration normal, but the total nitrogen low; the microscopic appearance showed no rarefaction of the cytoplasm, small cells and nuclei close together.

It would seem, therefore, that while a protein deficient diet will lead to a protein deficient liver, carbohydrate intake exerts a great influence on the histological appearance as well as on the nitrogen and glycogen concentrations. In the absence of carbohydrate intake (fasting) the cells, although they may appear superficially normal actually are small, the nuclei are close together and the cytoplasm is dense. Because of the decrease in the total liver nitrogen and the narrowing of the liver cords, this picture may be spoken of as atrophy. In contrast, with adequate carbohydrate intake the cells are large and the cytoplasm rarified, a picture which has often been referred to as hydropic degeneration.

CONCLUSIONS

Following protein starvation, the histological appearance of the liver as well as its content of nitrogen and glycogen depends upon the intake of carbohydrate. When the carbohydrate intake is high, the cells are large, contain little protein, and present a rarified appearance of the cell cytoplasm often called hydropic degeneration.

After a fast (absence of carbohydrate) the liver is just as deficient in total nitrogen because it is smaller, although the concentration thereof is normal. The microscopic picture may be called one of atrophy; the cells are smaller, the nuclei closer together and the cytoplasm dense.

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THE COATED TONGUE

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Throughout gastro-enterology, etiology has been, and remains today, an enigma. The causation of non-specific ulcerative colitis, of ileitis, of appendicitis, of duodenal and gastric ulcer, of gastritis, remains partly or wholly unexplained.

The everyday coated tongue, the mechanism of its formation, and its true significance, is surfeited with nebulous etiological doubts.

In attempting to explain the method of the formation of the coated tongue, any and every theory that has been forwarded can be denied by succinct criticisms. Negative facts are many, positive additions to our knowledge few. Is the coated tongue an isolated oral phenomenon? Is it associated with halitosis, and in what relationship? Is it like most of the other gastro-intestinal diseases, a disturbance of the autonomic nervous system, or is it again to be included in the category of psychosomatic manifestations? Is the coated tongue the mirrored reflection of the state of the gastric mucosa, or does the tongue announce the state of function or dysfunction of the intestinal tract?

The coated tongue is the most obvious single physical sign on inspection, yet the most obscure when one attempts to explain the mechanism of its formation.

In any study of the causation or the method of production of halitosis, the tongue, and particularly the coated tongue, must eventually come into consideration. In such an investigation of bad breath it soon becomes patent that the tongue plays little rôle; simple observations soon reduce the rôle of the tongue in halitosis to a minimum. Halitosis we believe to be entirely of internal origin (1) (2), based upon some disturbance in metabolism, or in intestinal absorption, probably related to fats and fatty acids. In true halitosis, the tongue is almost invariably clean. A person may have a coated tongue as a passing phenomenon and still have a perfectly usual or normal mouth odor. Many persons have habitually a coated tongue, but do not suffer with halitosis. Nor is a bad taste in the mouth necessarily associated with either a coated tongue or with halitosis. One may wake with a bad taste from the dietary indiscretions of the previous night; the tongue is not necessarily coated, nor is the breath particularly obnoxious.

In studying breaths, however, one does encounter occasional cases wherein a heavily coated furred tongue is associated with a persistent malodorous

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breath of a sour or variable disagreeable nature. Local hygienic measures in the nature of scrubbing the tongue locally will relieve such cases of their uncomfortable condition. Such instances are few and are probably dietary in origin.

THE NATURE OF THE COATING ON THE TONGUE

One soon becomes interested in the nature of the coating on the tongue and in its method of production. The coating on a tongue consists of bacteria, food particles, and debris deposited upon and in between the projecting papillae which line the surface of that organ. The filiform papillae are the most numerous of the small projections on the tongue, occupying the general area anterior to the large circumvallate papillae which form the inverted V-shaped terminal sulcus at the base of the tongue. Scattered variably throughout, but chiefly clustered at the edges, are arranged the fungiform papillae; the foliate papillae are seen occasionally at the edges and at the back of the tongue.

The filiform papillae play the dominant rôle in the formation of a coating on the tongue. They are arranged in rows parallel to and and in front of the circumvallate papillae; each filiform papilla is surrounded by projections, the "secondary" papillae which protrude like flexible spines or spikes, covered by stratified squamous epithelium. They contain no erectile mechanism of a muscular nature that can be demonstrated.

Sections of the coated tongue reveal the fact that the coating consists of debris and bacteria mingled with an excess of stratified epithelium on the tips of the filiform papillae (Dickinson) (3). The type of the bacteria found in the coat varies and is of no special significance. Fungi are often present in a coat of longstanding.

Using a magnification of seventy times, and staining the tongue in situ, Henning (4) was able to observe the living tongue surface. He found the filiform papillae to be plump round hillocks with transparent epithelium. Most characteristic were the secondary papillae which jutted out from the filiform papillae like blades of grass with serrations. When the tongue was coated the papillae were long, thick, firm, and tense, and were surrounded by leucocytes, bacteria and particles of debris. The secondary papillae contained thicker epithelium in those tongues which were coated and the epithelium was more hornified.

Other attempts to study the surface of the tongue, such as the preparation of "tongue prints" by reduplicating the coarser geography of the tongue on prepared paper (5), have not added more to the detailed knowledge of the coating of the tongue. However, it affords a simple division of all tongue surfaces into normal, coated, scrotal, or smooth. The various fissures and patterns of the tongue, including the so-called geographic tongue, are still without

action on the tongue; fluid diets, on the contrary, have little effect and permit, when long continued, the accumulation of a true tongue coating. The very obnoxious coating of the tongue and its concurrent halitosis during the administration of the Sippy diet for ulcer is explained by its liquid nature as well as on its basis of milk and of butter fat.

The rôle of a dry tongue or mouth. The relationship between dry tongue and diminished salivary flow was established by Dickinson (3); on cannulating the duct of the parotid gland in patients with dry tongue, he found definite evidence of diminished secretion from the parotid.

Diminution of saliva is alone insufficient to cause coating of the tongue. As in most conditions, many factors operating together are necessary to effect the final result. We were unable to produce coating of the tongue by administering atropine in large doses ($\frac{1}{100}$ gr. three times daily) for periods as long as a week and up to the point of tolerance. In these cases though the sensation of dryness in the mouth was marked, the tongue itself remained clean and moderately moist.

Is saliva odoriferous? In connection with saliva it should be pointed out that the salivary fluid contributes little or nothing directly to odors of the mouth. Saliva has no odor and transmits none. Organic compounds which are capable of permeating the salivary glands are relatively few and are those of simple molecular structure such as urea, alcohol, or acetone. For these to be present in saliva in sufficient quantity as to cause an oral odor would require a concentration in the blood to an extent that would yield a strong expiratory odor to the air exhaled from the lungs. The odor from the exhaled air would completely overshadow any odor excreted in the saliva. A substance like garlic, given per rectum, penetrates the salivary glands little if at all. Samples of saliva collected during the period when the breath is characteristically strong have in themselves no odor of garlic. If the salivary specimens are heated a faint odor of garlic can be detected. It is more likely that the odor entered the saliva from the odoriferous breath rather than that so small an amount of garlic was secreted into the saliva.

The rôle of fever. An increase in body temperature is often suggested as an important factor in coated tongue. Dickinson (3), in his interesting monograph, felt that this was the chief cause of coated tongue in febrile states. He compiled statistics to substantiate his claims, but in our observation the incidence of coated tongue in those with increased temperature was not much above the normal controls. Why increased temperature should coat the tongue is not clear. Some increase in the length of the papillae probably occurs as the result of increased flow of blood through that organ and of generally increased body metabolism. The general dehydration which occurs diminishes the flow of the saliva with the resultant loss of cleansing action.

The coated tongue of severe illness is a combination of temperature and of dehydration combined with decrease in the amount of salivary flow, lack of mechanical debridement due to relative degrees of inanition, and use of fluid instead of solid forms of nourishment.

II. The influence of the gastro-intestinal tract upon the coated tongue

The relationship which exists, or may exist, between disturbances of the alimentary tract and the tongue and its coating, is a subject which has led to much disputation. The tongue is classically pictured as the "mirror of the stomach." And yet the weight of evidence is much against this concept. Certainly there are no known conditions of the small or large intestines which can directly be related to the coated tongue. Even that familiar disturbance, constipation, is not in itself effective in producing coated tongue; Dickinson noted clean tongue in persons who passed 28 to 30 days without bowel evacuation.

"Constipation." Deliberately we produced constipation in a series of individuals for periods lasting three to nine days. By administering liberal doses of deodorized tincture of opium, we induced constipation but did not succeed in producing a thick or furred tongue, nor were the daily normal variations in the coats in any way unusual. One promising case developed a heavy coated tongue on the fifth day, but this disappeared on the seventh day despite the persistence of the constipation.

"Upset stomach." It cannot be denied that what is called an "upset stomach" is usually followed, in six to twelve hours, by a definite coating of the tongue. The "upset" is usually caused by indiscretions and is characterized by biliousness, slight distention, bad taste in the mouth, eructation, epigastric discomfort, and perhaps an abnormal breath odor. The correlation of the changes in the tongue with the disturbance in the gastro-intestinal tract is complicated by the lack of knowledge of what actually constitutes the latter changes in the intestinal physiology. Ignorance of the causes of the coated tongue runs together with ignorance of the more important primary factors at the lower levels. It is interesting to note that neither the vomiting of pregnancy nor of sea-sickness are associated with coated tongue; the vomiting of intestinal or pyloric obstruction is however invariably accompanied by a thick furred tongue. Severe cardiospasm with esophageal retention is associated with both halitosis and with coated tongue.

Gastritis. Gastritis, acute and chronic, is often designated as the cause of both the gastric disturbance and of the tongue changes, but this is a label about which little, as yet, is known. Pathological study of the mucosa of the stomach of deceased persons who, as an ante-mortem phenomenon have developed a heavily coated tongue, have not been fruitful (3).

Several attempts have been made to correlate the tongue picture with the gastroscopic appearance of the gastric mucosa. The results are at variance, just as are the interpretations of the gastric mucosa as seen through the gastroscope. Henning (4), in seven hundred cases in which a diagnosis of chronic gastritis was made, found the tongue coated in the major proportion of the cases. Chevalier and Moutier (8) stated that the tongue resembled the stomach in cases of gastritis. In ulcer and carcinoma cases, nothing of significance was found in the tongue (9) (10). Epithelial defects or shallow ulcers were said to be present on the tongue (11), but careful studies (9) do not substantiate this observation.

A more direct relationship exists between the atrophic, red beefy tongue and the atrophic gastric mucosa as seen in the deficiency anemias. In the glazed tongue of Addison's anemia the filiform papillae are involved in the atrophic process.

The rôle of the autonomic nervous system. Still another theory would explain the coating of the tongue as a manifestation of a vaso-motor disturbance associated with altered control by the autonomic nervous system. According to this concept, hyper-irritability or over-distention of the stomach produces reflexly a vaso-constriction of the vessels supplying the tongue; this relative ischemia causes a surface desquamation of the tongue epithelium, drying and coating the exposed area. Thus a reflex vaso-motor phenomenon is offered as the explanation of the coated tongue in dyspepsia.

THE COATED TONGUE AND THE THEORY OF DIRECT INTESTINAL RETROGRADE FLOW

The literature. Certain rather ill-defined facts and scattered clinical observations have suggested the idea that by some means of retrograde propulsion intestinal contents may reverse themselves and enter the stomach and the pharynx. Nervous and emotionally disturbed individuals, almost always women, have reported the ability to taste and to recognize the odors of nutrient or therapeutic enemata (12). McLester (13) quotes instances where, after an unbelievably short period, nutrient enemata were brought up as vomitus. It is not an uncommon phenomenon in the experience of any one during a routine barium enema, to note under the fluoroscope the rapid filling of the small intestine. Overfilling of the colon with the barium clysma, and the relaxation of the ileo-cecal valve, may result in retrograde peristaltic rushes that may fill the small intestine even up to the duodeno-jejunal angle. Alvarez (12) has seen, under experimental conditions, the same phenomena in cats when the colon has been filled with fluid under pressure and the rectum has been tied off.

While such phenomena in the human person under conditions of health or of disease are quite unusual, one must concede the fact that they may occur.

While at first we were most skeptical of the fact that nutrient enemata could be tasted by even hysterical women, closer observations and questioning have brought to our knowledge two instances in nervous women where the use of peppermint or of turpentine in evacuation enemata was discontinued because of the disagreeable taste so promptly induced.

Can such unusual and exceptional phenomena possibly suggest an explanation for the common coated tongue? Grutzner (14) experimentally recovered from the stomach of animals and of persons materials which he had placed in the rectum. These materials included colored fluids, charcoal particles, lycopodium powder, cornmeal, and finely divided horsehair. He found that these materials passed upward in the intestinal tract only if the tract was completely emptied by previous catharsis or enemata, and if the materials were suspended in saline and not in a purely aqueous suspension. He elaborated the theory that this retrograde progress was governed by chemical influences and was carried out by fine movements which were independent of the major aboral peristaltic activities of the intestines.

These interesting experiments were repeated by various observers with violently opposing results (15) (16) (17). As late as 1929 Maley (18) refuted the observations of Grutzner (14), because in twenty experiments with humans he failed to obtain any positive evidences of intestinal retrograde propulsion into the stomach.

The whole thesis was brought directly home to the problem of the coated tongue by the observations of Kast (19), who attempted to recover on the tongue materials ingested. To avoid tongue contaminations the patients swallowed closed capsules containing lycopodium spores, all dental and lingual contact being sedulously avoided. In seven out of eleven trials he succeeded some hours later in recovering the spores on the scrapings of the dorsum of the tongue.

The experiments of Grutzner (14), the clinical observations of Alvarez (12), and the highly pointed lingual tests of Kast (19), when linked together offer a simple, almost obvious, explanation of the coated tongue as based upon retrogressive flow of intestinal and gastric contents.

The results of our experiments. Some of these simple experiments and observations were therefore repeated by us, utilizing as test material normal persons or patients free of gastric and intestinal complaints. The rectum was thoroughly cleansed the previous evening by means of enemata; in the morning, with the patient in the fasting state, various substances were inserted in saline suspension for rectal retention. At the same time, a Levin tube was inserted into the fasting stomach and frequent gastric withdrawals at fifteen minute intervals, were made during the following hours. When instilled per rectum, neither lycopodium spores, nor charcoal, nor reduced iron powder

could be recovered at any time from the fasting gastric secretions. However, better success attended our efforts when lithium carmine (five to ten grams in 100 cc. saline suspension) was used as test material. Ten experiments were carried out on various persons; in four of these experiments the lithium carmine was readily recovered from the fasting gastric contents within five to six hours of the time of its insertion into the cleansed rectum. In about five hours the fasting gastric secretion became distinctly, though faintly, red, remaining so for another two to four hours. Such fasting specimens when sedimented showed under the microscope the characteristic particles of lithium carmine and their identifying color. In one case, that of a patient who had had a partial gastrectomy for ulcer with a Balfour anastomosis, the carmine inserted per rectum appeared in the stomach in two hours.

Encouraged by the results of these latter experiments, we attempted to repeat those of Kast (19), hoping now to link up the stomach with the tongue and the mouth. Patients swallowed capsules at night containing lycopodium spores; in the early morning the tongue was observed and scraped, the scrapings from the tongue and the washing from the mouth being examined for spores. In no experiment and at no time could lycopodium, given into the stomach by capsule or by tube be recovered next morning or at any time thereafter from the surface of the tongue.

SUMMARY AND CONCLUSION

We were thus stymied in our attempt to explain simple coated tongue on a basis of direct retrogression of gastric or intestinal material. True, we were able to demonstrate under exceptional conditions the retrograde transport of colonic content as far as the stomach. But to succeed in even four out of ten experiments certain conditions had to be met; the alimentary tract of the subject under observation had to be cleansed and empty and at rest. Only lithium carmine could be utilized for successful demonstration and that only in saline suspension. Obviously these conditions are not often met in clinical observations. Coated tongues occur in persons who have overloaded and abused their digestive tract rather than under conditions of austere fasting.

But conceding the fact that under circumstances the retrograde activity will transport the content of the rectal ampulla as far as the stomach we were absolutely unable to bridge the gap from stomach to tongue. Under pathological conditions of cardiospasm with esophageal retention the tongue is usually coated and the mouth odor fetid. But this is definitely a pathological mechanism and cannot in any manner alter our conclusions and experiences under normal physiological conditions.

We are therefore forced to fall back on the only tenable hypothesis, namely, the concept that the coated tongue is an intrinsic lingual phenomenon, analo-

gous to one of the precision meters in the cockpit of a plane, which reflects altitude, speed, temperature, and in general physical conditions in the body of the moving mass. Reflexly, through the anatomic nervous system, by means of deviations in vaso-motor control, the tongue reflects the state of hydration in the body, the conditions of digestive activity in the alimentary tract, the general health of the individual. The delicate filiform papillae act as the bell-wether of the body politic, raising themselves to gather mass and debris when all is not well; smooth and velvety and clean when conditions are appropriate for health and normal function.

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ON CHRONIC EPIGASTRIC DISTRESS AND ITS RÔLE IN CHRONIC GASTRITIS: AN ANALYSIS OF THE PROBLEM[1]

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Does chronic gastritis cause symptoms, and if so, what are these symptoms? This is our subject today.

It is a difficult subject, because the old, difficult question of the mechanism of distress is involved. In patients who have epigastric distress, we believe, we see gastroscopically inflammatory changes of the stomach. But are these apparent changes the cause of the distress? These changes look very striking to us because we are accustomed to see daily gastroscopic pictures; they are almost meaningless to the occasional on-looker.

I will show you later that they correspond exactly with well defined anatomic changes. Nevertheless, it has been objected that the epigastric distress of the patients has nothing to do with these definite anatomic changes; it has been thought to be of nervous or psychic origin. Is this true, or do the anatomic changes cause the distress? This question must be answered if we want our knowledge of the existence and frequency of chronic gastritis to be of value for our soldiers and sailors suffering from epigastric distress.

POSSIBLE CAUSES OF EPIGASTRIC DISTRESS

We may try to approach these difficulties by stating clearly the different possibilities which have to be considered in a patient who tells us that he has epigastric distress, such as pain, pressure, fullness, etc.

There are 4 possibilities: I. Malingering; II. purely psychogenic distress; III. disturbance of function; IV. anatomic disorder. The last two obviously are interdependent.

I. Our patient may say that he has distress, but the truth is that he has no distress. Then he is a malingerer. Such patients are seen frequently in the European compulsory health insurance and we may see them in the Army and Navy.

II. Secondly, the patient may experience distress, but may have neither any alteration of the anatomic structure nor any disturbance of function. Theoretically we may believe that such purely psychogenic distress does exist; but here we face the first difficulty; we can not prove it. There is no way to differentiate between psychogenic distress and distress caused by psychogenic disturbances of function. Still worse; we are uncertain regarding the presence of some hidden undetectable anatomic lesion which may cause symptoms.

[1] Presented at the meeting of the American Gastroscopic Club, Atlantic City, June 7, 1942.

Some of you still remember how often "nervous dyspepsia" was formerly diagnosed instead of duodenal ulcer; we also know that this diagnosis is still made even though the anatomic changes of chronic gastritis are present, and we never know whether or not some undetectable inflammation of the small bowel or of the pancreas may be present, or even only anatomic changes in the nerves or in the ganglia which we can not discover.

I believe that there are cases of purely psychogenic distress, but this diagnosis should never be made merely because the patient has some psychoneurosis and no detectable alterations of function or structure. I would allow myself to admit that psychogenic distress is present only if there is a direct connection between the psychic disturbance and the site of the symptoms, in the sense of the so-called symbolism of the organs, or if there was coincidence of a psychic traumatism with an acute transitory organic disease. In such a case the psychogenic symptoms remain attached to the organ although this in the meantime has been cured anatomically. Errors in this realm are frequent and should not be committed in favor of psychoneurosis.

III. The third great group of causes for epigastric distress consists of disturbances of function which may be disturbances of motility, such as spasm or atony or hyper-motility, or disturbances of secretion, or disturbances of absorption. These disturbances of function may be due exclusively to psychogenic factors.

Here we are on somewhat firmer ground. We know that emotion before appearance on the stage or before an examination may result in hypermotility of the intestine, in diarrheas which later never recur. We know that strong emotions normally may lead to spastic contractions of blood vessels, causing pallor of the face in fear.

But similar disturbances of function may be caused by distant somatic disease. "Neurogenic shock" is characterized by vasodilatation and yet it is due to somatic traumatism. The obstipation seen so often in ulcer and in gall bladder disease has often been explained by the assumption of reflex spasms. Reflex spasm may also occur in chronic gastritis. A dysfunction of the bowel may occur reflexly from an inflamed gastric mucosa.

IV. We have approached our fourth and last great group—the disturbances of anatomic structure, or organic disease.

From ancient times we have been accustomed to accept primarily the conclusion that a demonstrable organic disease causes the distress complained of. This short circuit conclusion: Here organic disease, there distress caused by this disease, has enabled us to develop the amazingly differentiated symptomatology and diagnosis of organic diseases. We should not give up this solid foundation of internal medicine without urgent necessity in any field of medicine.

WHY DO SYMPTOMS APPEAR AND DISAPPEAR?

Psychological explanation. At this point a personal remark may be permissible; it will partially explain my attitude. After the first World War from 1919 to 1923, I was a psychotherapist, carrying out all types of psychotherapy, hypnosis, catharsis and analysis. I know both sides of the question and that is why I dare to sustain the old, anatomic conception of the origin of distress. In the medical "Weltanschauung" in the 19th century there was no place for any other thinking. The "soul" was practically non-existent because it was not found at autopsy, a famous dictum, as you know. But then the "soul" was rediscovered and the pendulum swung back. It even swung back all the way, since there is a small school the desciples of which now believe that only the "soul" should be considered and that "the body is always secondary." This is the formulation Thomas Mann gives this way of thinking in his "Magic Mountain." However, the majority of us agree that there are diseases of the "soul" and that there are diseases of the body, and that often the disease of the "soul" will react on the body and often the disease of the body will react upon the "soul." But many, I am afraid, have been so over-awed by the discovery that there is a "soul" that they now have a great tendency to forget the importance of the body. Often, however, the body—the combination of anatomic lesion and disturbed function—is entirely in the foreground of the clinical picture as for instance in mass accidents and war wounds, and in many other cases in which anatomic lesion and distress jointly originate, persist and subside. And yet, even these diseases are influenced by the "soul": Often hypnosis has cured transitorily a severe toothache. We must realize that the symptoms of every organic disease are affected by the condition of the "soul." A case of constant vomiting may be cured by hypnosis, yet the patient may have a brain tumor and die from it. Certainly many of us have observed a patient with a gastric carcinoma, suffering from pain and complete lack of appetite; after an unsuccessful laparotomy he is told that everything is fine, and now suddenly his pain is gone, his appetite comes back and he will live rather comfortably until his death. A gall bladder attack may be caused by a heavy meal, but it may be caused as well by an emotional upset. The salutary effect of the entrance of the physician into the sick room is well known to you. Thus distress symptoms are regulated continuously by the "soul." The relation between the distress picture and anatomic change is a variable one, depending upon the sensitiveness of the patient, and—in the same patient—upon the special condition of his "soul." Therefore we can understand without any difficulty that distress can disappear transitorily and recur although the anatomic picture remains unchanged. This we see in gall bladder disease and in gastric ulcer and in gastric carcinoma. We see it frequently in gastritis. Be-

cause of this continuous regulation of the distress picture by the "soul," there is no reason why we should assume that the symptoms are not caused by the anatomic changes present.

This is one explanation as to why symptoms of an anatomic disease may disappear and recur.

Anatomic explanation. Another equally important one is the purely anatomic explanation. The anatomic picture may change. An esophageal carcinoma, growing painlessly at first, will produce pain as soon as it penetrates through the esophageal wall. Pain in pulmonary tuberculosis will occur when the anatomic process involves the pleura and may subside if this involvement subsides. In chronic gastritis exacerbation of the anatomic picture, characterized especially by edema, may produce a recurrence of the distress picture, sometimes after years free of distress. We know from early studies of Friedenwald and Morrison (2) that almost every case of untreated pernicious anemia has abdominal distress at some time. However, after treatment there usually is no abdominal distress present. It may well be that the return of the normal composition of the blood, due to the treatment, reduces the susceptibility of the gastric mucosa to irritation; the acute inflammatory reaction, especially the edema, may therefore disappear, and with it the distress; the consequent atrophy naturally will not disappear, but will not cause symptoms.

Thus we have found two different explanations for the fact that in many chronic diseases, such as chronic gastritis, symptoms will disappear and reappear. There remain a few objections to the concept of symptoms caused by the anatomic alterations of chronic gastritis, the validity of which must be discussed.

CAN CHRONIC ATROPHIC GASTRITIS CAUSE SYMPTOMS?

A research problem. Some critics have argued that chronic atrophic gastritis can not possibly cause symptoms. They have thought only of the lack of function and have compared patients with an atrophic stomach with patients who have had a resection of the stomach. These patients have no important symptoms; how then, should patients with an atrophic gastritis have symptoms? These critics have thought only of the lack of function and have forgotten the inflammatory edema so regularly present in atrophic gastritis, which probably is the chief reason for the symptoms. Other critics have argued that chronic gastritis can not possibly cause symptoms, since large gastric carcinomas often cause no symptoms. This is an obvious fallacy. Distress does not depend upon the extent of a lesion. It even does not depend upon the miscroscopic character of the lesion. A large carcinoma of the skin may not produce any pain. A small boil will. A small lichen eruption of the

skin will cause itching, but a similar lesion will cause no itching, when of syphilitic origin. Neither extent nor structure are solely responsible for the distress, but probably some chemical tissue reaction of unestablished kind and origin. Do we say that the lichen papula can not produce itching because the similar syphilitic lesion does not? We don't. We admit that the lichen papula does cause symptoms and consider the question as to why as a research problem. The same conclusion should be drawn if we find undeniable microscopic changes in the gastric mucosa either with symptoms readily attributable to these changes, such as vomiting or distention pain, or without symptoms. Why these changes sometimes are connected with symptoms, and sometimes are not, is a research problem.

GENERAL SYMPTOMS

Slightly more difficult is the discussion of general symptoms, for instance in atrophic gastritis. It has been said that they must be psychogenic because a patient may not have such symptoms after a gastric resection. Let us assume for a moment that general symptoms such as tiredness do occur in atrophic gastritis. It may not be true, but let us assume it for the sake of argument. Then immediately the door is open for much speculation and much research as to why such symptoms may develop.

The normal gastric mucosa shows very little absorption; but perhaps the atrophic mucosa is permeable for products of digestion which can not penetrate either the normal gastric wall or the normal intestinal wall and which may produce harmful effects when permitted to enter the tissue and the blood? Henning (4) has proved that an aqueous solution of potassium iodide is absorbed only from the gastritic mucosa. LeVine and Kirsner (6) have found that phenolphthalein is readily absorbed in cases of atrophic gastritis. No other studies have been made on this important subject, and to the best of my knowledge no studies have been made on the various aspects of body metabolism in gastritis, except that the enigmatic Russell bodies found only in atrophic gastritis were found by Moutier (9) to have something to do with the iron metabolism. Perhaps, the pathological gastritic mucosa itself may produce toxic substances. Much work has to be done to find out what really causes the symptoms; but it is not permissible to deny primarily the connection of the symptoms with the organic alteration.

After having discussed the fact that the "soul" may cause and affect bodily distress, we have to recall that organic disease may influence the "soul." It is obvious that blindness or deafness alter the mental reactions of a patient. Chronic diseases of the internal organs sometimes cause definite psychic reactions. The euphoria of the terminal stage of lung tuberculosis is well known. In our own field we continuously are surprised about the attitude of patients

having a beginning gastric carcinoma; they have an almost psychotic tendency to minimize their complaints and to delay thorough examination. Perhaps the symptoms of chronic gastritis may be considered in a similar light. One sometimes gets the impression that chronic gastritis by its very existence leads to a hypochondriac attitude. This, of course, may be favorably influenced by psychotherapy, although its cause is a purely anatomical one.

Thus we have seen that it is not permissible to call the symptoms of chronic gastritis psychoneurotic symptoms, and I believe it is dangerous to call them psychoneurotic symptoms. Why dangerous?

Since the end of the last War, we have learned to study and to understand psychoneuroses. We have freed them from the contempt which adhered to them before. We realized finally, that they were subconscious escape mechanisms, but we often thought such escape justified. If an exceedingly gallant officer (I am referring to an actual case) after his seventh wound received in his fourth year of war, developed psychoneurotic symptoms, then we knew that he wanted to continue to do his duty at the front, but that his limit had been transgressed. In order to cure him we had only to tell him that there is a limit of enduring hardship and wounds even for the most courageous man, that seven wounds were enough, and that he must be used somewhere at home. In such a man we even admired his psychoneurosis.

But, in my opinion, later we went too far. We permitted indulgence in such escape mechanisms and viewed them as natural reactions. We cannot deny that medicine is partly responsible for the "softness" of the last twenty years and for an education which favored unrestricted self expression, the voicing of the own little individuality which seems to me in contrast to true American tradition. I am sure that the pioneers would not have had a good understanding for our escape mechanisms. And we may be just as sure that our soldiers and sailors will develop again just the same attitude. They will appreciate again that value, which during the time of softness, was not sufficiently kept in mind: namely, that it is an essential quality of the character of a man to resist escape and to "keep soul and body together" in the face of stern realities. Therefore, at present, a medical officer should consider the character of his patient and recall that for this patient the term "neurosis" will have the old odium again. Rarely will the gallant soldier tolerate being labelled as a neurotic. I do not believe that he, when suffering from abdominal distress, will like to be put into a separate hospital department for neurotics as recommended by Sir Arthur Hurst (5). So was the attitude of the soldier in the last war. You infuriated every soldier and made him a virtual mutineer when you dared to call his disease a "nervous" one. He knew nothing about the theory of neurosis, but he did know that the label of neurosis would accuse

him of a certain mental deficiency, or of a quality of character which through all the ages has been called by the name of cowardice.

Therefore, if we believe that in our field there is much less reason to admit psychogenic distress than is often thought, it is certainly justified to warn not to label a patient as a neurotic if an organic disease is present. The term "nervous dyspepsia" would be wrong, it would insult the man and it would be against the spirit and the interest of the Army.

HISTOPATHOLOGICAL PICTURE OF CHRONIC GASTRITIS

Now let me turn to my demonstration which will give you the proof that chronic gastritis has a definite *histopathological picture*, and that there is a definite relationship between microscopic and gastroscopic pictures.

In order to obtain unobjectionable microscopic material of the gastric wall two methods had to be considered. The first one, that of gastroscopic biopsies, was used with great success by Swalm and Morrison (11). I thought that such biopsies would not yield sufficient material to permit the development of a comprehensive histopathology of chronic gastritis; therefore, Dr. Ortmayer and I chose a second method, namely, that of taking biopsies from the entire gastric wall at laparotomies without the use of ligatures and clamps and with immediate fixation of the specimens. The best place for taking the biopsy was determined by preceding gastroscopy and in some cases additional fresh autopsy and resection material was used, namely, from cases of histamine-proved anacidity. This material, now consisting of 52 sections of gastric walls, permitted the establishment of the histopathology of chronic gastritis and the determination of the reliability of the gastroscopic method.

Our results differ somewhat from those of Swalm and Morrison. This may be due to the different material used or to the different gastroscopic interpretation or to both factors. Summarizing our results we come to the following conclusions: The normal range of infiltration and proliferation of the antrum is not well known, but the normal histology of the mucosa of the corpus is well established. If gastroscopically we diagnose a normal mucosa, we may—though rarely—commit an error. Mild inflammatory changes may be present, and once severe atrophy was overlooked. If gastroscopically the diagnosis is chronic gastritis, then invariably, not mild, but severe outspoken inflammation was present microscopically, usually of the type described gastroscopically.

The microscopic structure of the body mucosa has been well described by Maximow and Bloom (8). It should be stated that the amount of connective tissue between the pits varies somewhat; it contains lymphocytes, fibroblasts, rare leukocytes and very scant plasma cells. An occasional plasma cell, therefore, it not pathological, but numerous plasma cells certainly are. It should be realized that the tall columnar, surface epithelium is very regular, the oval

nuclei lying regularly in one row in the lower third of each cell and mucus being found in the upper third of the cell (these statements are valid only for the fasting stomach). The multiple nuclei often found in one parietal cell; 2, 3, 4, or 6 are not pathological. The bottoms of the long body glands touch the muscularis mucosae, but at this point small accumulations of small round cells, which are not pathological, are sometimes found.

In every case in which a superficial gastritis was gastroscopically diagnosed a different picture was found. The most important feature of this disease is the outspoken and sometimes tremendous edema between the pits. There is a fine fibrinous net within this edema fluid, free red blood cells and large hemorrhages are seen. If we see this edema and consider the distribution of sensible nerve endings in this region and between the cells of the surface, then we have to admit that not the presence, but the absence of distress would be puzzling. The edema sometimes becomes so severe as to cause compression and flattening of the surface epithelium. The plasma cells are definitely increased in number. Hemorrhagic gaps in the continuity of the surface epithelium are seen; these probably are not artefacts. Sometimes the cells of the surface epithelium are filled entirely with mucus which compresses the nuclei and even excavates them.

The transition from superficial into atrophic gastritis, so well known to the gastroscopist, is also found histologically. The plasma cell infiltration becomes intense and due to its pressure at the neck of the gland retention cysts form at the bottom of the glands. Proliferating infiltration destroys the glands and sometimes large irregular lymph follicles will be seen. The pits start to proliferate, to become tortuous and branching, and during this proliferation the surface epithelium and the epithelium of the pits undergo sometimes a metaplastic change into an intestinal type of epithelium with goblet cells and Paneth cells. Russel bodies are frequently seen in the interstitium. Proliferation of the surface epithelium may appear, and this has been called by Konjetzny "atrophic-hyperplastic gastritis." All these changes are seen in pernicious anemia, as well as in cases of atrophic gastritis without a deficiency state. Hence, it follows that at some stage of pernicious anemia a definite inflammation of the gastric mucosa is present showing alteration, proliferation and especially exudation which is most marked. I believe we are forced to call such a condition inflammation, not merely degeneration, but I shall not go into the question why in deficiency states inflammation is present. In the end state of both, i.e. atrophic gastritis with and without a deficiency state, the entire mucosa is gone, the surface epithelium almost rests on the muscularis mucosae; this, then, is an atrophy consequent to a preceding inflammation. The fact, however, that at gastroscopy we can see the large submucosal blood vessels in atrophic gastritis does not depend upon this thinning, as was thought formerly, at least not in the body. The blood vessels are readily seen in cases

in which exact microscopic measurement does not reveal any reduction of the mucosal thickness. The opaqueness of the normal mucosa, as Bensley (1) has shown, is dependent mainly upon the presence of the opaque chief cells. If they are gone at an early stage of atrophic gastritis, the mucosa becomes transparent. If at gastroscopy we diagnosed atrophic gastritis, then we invariably found microscopically severe outspoken pictures, never mild or questionable ones. It follows that we, in Chicago, do not diagnose atrophic gastritis frequently enough. It follows further that Ruffin's (10) concept, that we might simulate atrophic gastritis at gastroscopy by overdistention of the stomach, is not correct, and that Gutzeit (3) was right when he considered maximal distention to be indispensable for the discovery of atrophic gastritis. The posterior wall of the stomach can not be distended much, and I feel that here we often overlook atrophic gastritis.

HISTOLOGICAL TYPES OF HYPERTROPHIC GASTRITIS

If we define hypertrophic gastritis as chronic inflammation of the entire gastric mucosa without reduction of the glandular apparatus, then we find microscopically three different forms. There may be a transition between them, but it seems that they are not related to atrophic gastritis. These findings are in contrast to Lubarsch's (7) original concept of chronic gastritis as a progressive hyperplastic-atrophic inflammation. The *first form* may be called interstitial hypertrophic gastritis. We see small cell interstitial infiltration and a reaction of the lymphatic tissue, but only a little proliferation of the surface epithelium. In the *second form*, which I would like to call proliferative hypertrophic gastritis, the glandular portion of the mucosa is of normal structure and thickness, but on top of this glandular layer we find a grotesque proliferation of the surface epithelium. The epithelial cells are decidedly pathological. They lose their capacity of forming mucus, the nuclei lie in several irregular rows; true cell syncytia are formed. In the *third form*, which perhaps could be called glandular hypertrophic gastritis, the mucosa at the first glance looks quite normal, in spite of the development of large nodes which in contrast to the nodes of the normal mucosa have no stalk. But exact measurement shows that the diameter of such a mucosa is tripled and that there is a tremendous pathological overgrowth of the whole glandular apparatus. One would be inclined to call this mere hyperplasia, if at some places signs of inflammation, such as cysts filled with leukocytes, edema, and cellular infiltration were not found.

SUMMARY

After having shown the importance of making the correct diagnosis of chronic gastritis, I hope I was able to convince this audience that the histopathology

of the disease is well established. It can be diagnosed reliably by gastroscopy, and thus, I believe we have now the right to proceed with the description and evaluation of the symptoms caused by chronic gastritis.

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CHRONIC NONSPECIFIC GASTRITIS: SIGNIFICANCE AS A CLINICAL ENTITY[1]

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I appreciate the invitation to participate in the scientific program of this, the première of your newly formed organization. I regard the occasion as auspicious and historic because Dr. Schindler, the outstanding figure in the development of modern gastroscopy, has played such a prominent rôle in the formation of the club.

We are all aware of the fact that chronic nonspecific gastritis has been one of the most important and controversial aspects of gastro-enterologic medicine in this country for the past six or more years. Moreover, some of the outstanding members of our profession do not regard the condition as of great importance. Neither has such skepticism been minimized by the observations of some of the small army of recruits to this field of endoscopy, which are understandable and inevitable in the presence of a scientific discovery or diagnostic procedure of great promise.

Yet in all fairness, there is some justification on the part of those who do not share your viewpoint wholeheartedly. We have been told to consider chronic gastritis as the commonest organic disease of the upper part of the digestive tract, a condition with which the rank and file have had only a speaking acquaintance at the most. Crohn (1) has voiced the feeling of a large body of the profession in the following manner: "The transition is too radical and extreme to permit such a reversal of all previous concepts without deliberate and cautious study, not only by the instrumentalist but by the body of observing physicians and pathologists."

The circumspect, somewhat critical physician gets the impression that gastroscopy is largely a subjective diagnostic procedure because of the personal factor involved in the interpretation of the endoscopic picture; that the disease, if such exists, has no characteristic symptomatology, no distinguishing gastric secretory pattern, no tangible physical or roentgenologic signs; and last but not least, that the histologic evidence on which conclusions are based is yet quite incomplete or is incompatible with other manifestations. Moreover, the endoscopic examination is limited to the surface of a highly vascular organ, possessed of a complex physiologic mechanism which is influenced by extrinsic as well as intrinsic factors. He gets the impression that our knowledge of gastritis is only in the formative stage, is quite incomplete and has many controversial aspects, and that what is accepted as factual by the gastroscopic

[1] Presented at the meeting of the American Gastroscopic Club, Atlantic City, June 7, 1942.

fraternity is based largely on the studies of relatively few experienced workers in this field. And to make "confusion worse confounded" some pathologists have expressed their opinion on the subject rather forcibly, probably with more heat than light. One colleague recently stigmatized the voluminous writings on the subject as "a curious excess of speculation, arbitrary conclusions and disturbing contradictions." In the same breath he also took exception to the use of the term "chronic gastritis" without qualifying adjectives.

But in the light of certain concrete facts gleaned from actual experience over a number of years one does not have to take these somewhat forbidding generalizations too seriously. Most of us gathered here today have long been familiar with various indisputable forms of gastritis and under circumstances which permitted histopathologic verification. I have reference to phlegmonous gastritis, acute and subacute ulcerative gastritis found at operation in association with gastroduodenal ulcer, the fatal hemorrhagic toxic gastritis of the bootleg, prohibition era, atrophic gastritis of pernicious anemia, subacute combined sclerosis, sprue and pellagra, and the ulcerative and atrophic forms of syphilitic gastritis. The pathologic museum contains specimens of entire stomachs with chronic diffuse gastritis, chiefly of the atrophic and hypertrophic varieties in association with, or secondary to, disease of the circulatory, hepatic and pulmonary systems. Chronic forms of primary gastritis and duodenitis and secondary forms of gastrojejunitis with their surgical and pathologic verification have come under our observation repeatedly for a quarter of a century. These forms, particularly the last two, were the subject of a thesis for the degree of Master of Science eleven years ago by one of my associates, Dr. Rivers (2). His paper would repay reading in the light of subsequent developments. Six years ago I (3, 4) reported a series of ten cases in which the condition was verified histologically, presenting roentgenologic defects of a chronic inflammatory process of the antrum in nine and of the duodenum in one. This form of gastritis, regarded as infrequent by the professional gastroscopist, was the subject of a symposium at a meeting of the International Congress in Brussels in 1935. Flörcken (5), Konjetzny (6), Crohn (1) and Golden (7) have reported similar cases. Until studies in progress have been completed I distinguish this type from the commoner instances of hypertrophied pylorus of adults, of which a considerable number have come under our observation.

I wish to call your attention at this time to one type of secondary gastritis which is as instructive and convincing to the internist and surgeon alike as it is rare. I have reference to those cases of hemorrhagic gastrojejunitis as a late sequel to gastro-enterostomy performed in infancy for congenital pyloric stenosis. Four of such cases have come under our observation in recent years, three of which have been reported by Walters (8). Recurring massive hemorrhage was a feature common to all and the only manifestation of the disease in

three. Gastroscopic examination afforded the sole means of accurate preoperative diagnosis. Finally, a serious form of gastritis, that persisting or following gastric resection, especially for duodenal or anastomotic ulcer, comes in review. There is no doubt about the existence and significance of this type and some of the others that I have just described. While such lesions may give rise frequently to a variable train of symptoms, they do, however, present an invariable unmistakable gastroscopic and histologic picture.

THE INDISPENSABILITY OF THE CONCEPT OF CHRONIC NONSPECIFIC GASTRITIS

Speaking solely from the standpoint of the clinician, I look on the indispensability of the concept of chronic nonspecific gastritis to clinical medicine as a certain famous European statesman once regarded the importance of the Austro-Hungarian Empire to the political stability of Europe; that is, if such empire did not exist, it would have to be invented. Perhaps I can make myself more clear by saying that no condition other than gastritis, either organic or functional, could logically explain a certain number of gastric disorders which we continually meet with in daily practice.

I am remainded of the circumstances which led to the recognition of a little known entity a quarter of a century ago, namely, gastric syphilis. Possessing the advantage of an unusual material coming annually under observation I was able to separate from the run of the mine, taken for granted, cases of gastric carcinoma a small group by virtue of an unusual combination of symptoms and signs. The majority of these eventually turned out to be instances of gastric syphilis. My immediate associates and I soon became sufficiently proficient in the recognition of this admittedly rare group so that we could predict with considerable assurance the presence of systemic syphilis on the basis of data pertaining solely to the stomach. Thus by a process of discriminate elimination, so to speak, one achieves clinical orientation which enables one to recognize an unfamiliar disease entity.

But far more common than such an entity are the host of patients suffering from a consistent disorder in the upper part of the abdomen, however irregular its symptomatology, that to the trained observer bespeaks its gastric origin. Roentgenologic examination almost invariably fails to disclose the presence of a gross lesion in the stomach or duodenum and evidence of cholecystic, appendiceal or pancreatic disease or diaphragmatic hernia is wanting. Neither is it obvious that the patient is psychoneurotic, toxemic or allergic. Under such circumstances gastroscopic examination frequently reveals pathologic changes confined to the gastric mucous membrane. Three and a half years ago my endoscopic colleague, Dr. Moersch (9), stated that he was impressed by the increasing skill with which his gastro-enterologic associates are able to recognize cases of chronic gastritis clinically.

In my judgment, the modern gastroscope, as all other endoscopic instruments in capable hands, has greatly widened our diagnostic horizon so far as the stomach itself is concerned. Today we are no longer content in labeling individuals nervous dyspeptics in whom routine examinations disclosed nothing definite. Neither are we content to submit patients to operation for some unexplained gastro-enteric hemorrhage, as was formerly the custom, often to the embarrassment of clinician and surgeon alike, without careful endoscopic study. In fact, such examination is indicated in every dyspeptic in whom roentgenologic examination fails to disclose a gross lesion of the stomach or duodenum and in whom the commoner extrinsic causative features have been excluded.

The following report of a case is illustrative not only of the paramount importance of endoscopic examination under certain circumstances but of the fact that an inflammatory lesion of the gastric mucous membrane may be the sole underlying cause for a chronic recurring condition:

Case 1. A white man fifty-three years of age entered the Mayo Clinic January 28, 1942. Nine years previously he had begun to have periods of epigastric distress, which appeared two or three hours after meals and were relieved by eating, as well as an intolerance for fatty foods. Two years after the onset of these symptoms he noticed tarry bowel movements for several days. In June, 1939 he had been hospitalized because of another more severe attack of bleeding, having both hematemesis and melena, with resulting syncope. At that time cholecystographic and bariumized meal studies failed to reveal any frank evidence of disease. Operation, however, had been performed, at which time a stoneless gallbladder had been removed, and the stomach and duodenum had been reported to be normal. A year later (July, 1941) this patient again had passed tarry stools, followed in a few days by epigastric pain of sufficient severity that an acute perforation of an ulcer was suspected. But at a second operation nothing had been found other than adhesions. In January, 1942 melena was experienced again but he was otherwise free of gastric disturbances. On physical examination moderate anemia was noted, the hemoglobin per cent being 66 and red blood cells 3,331,000 per cubic millimeter. Free hydrochloric acid was absent with the Ewald meal stimulus on fractional analysis. After stimulation with histamine there was a delayed appearance of the acid and the maximal acidity did not exceed 20 clinical units. The amount of secretion withdrawn at ten minute intervals was scant, ranging from 3 to 6 cc.

Roentgenoscopic examination of the stomach and duodenum at the clinic did not disclose anything abnormal. Gastroscopic examination revealed severe diffuse hypertrophy of the gastric mucosa with sufficient evidence of gastritis to account readily for the hemorrhages, although actual evidence of submucosal hemorrhage or ulceration was lacking. The patient was sent to the hospital and treated for three weeks with daily lavages of a silver preparation (targesin), with extralin, and with colloidal aluminum hydroxide given orally; also he was given a diet of a bland, high-

vitamin type. His general improvement was satisfactorily prompt and marked and he is now due to return for re-examination.

In a previous communication I (10) have reported on the various types of gastritis encountered, for which there was gastroscopic or histologic verification, or both. We have been particularly impressed with the ulcer-simulating group. Epigastric pain and discomfort, which usually have some relation to the time of eating, and from which relief by food or antacids is less consistent and effective than in cases of ulcer, are outstanding symptomatic features of gastritis. Hematemesis and melena alone may signalize such cases. Bleeding occurred in approximately 33 per cent of our cases. The asymptomatic nature of many verified cases of chronic gastritis, at least so far as the stomach itself is concerned, requires emphasis. A familiar example is gastric atrophy or atrophic gastritis of pernicious anemia and subacute combined sclerosis. Figure 19 in Faber's (11) admirable monograph is illustrative of extensive chronic polypous gastritis in an elderly woman who never had experienced digestive disturbances. Frequently, too, the only evidence of the disease is hemorrhage. This reminds me that another condition rivaling chronic gastritis in these respects is benign tumor of the stomach. On the other hand, unhealed gastric or duodenal ulcers, especially the latter, are much more likely to give rise to symptoms, although instances of painless hemorrhage in the presence of such lesions are not as infrequent as is generally supposed. Morlock and I (12) have pointed this out in a previous communication.

SOURCES OF ERROR

There is real need for caution in attributing undue importance to minor gastroscopic changes in relation to existing symptoms, as pointed out by Jones (13). Perhaps most important of all is to avoid the error of overlooking other lesions, often more sinister, in the presence of gastritis. I, personally, committed this error in two cases of atrophic gastritis. In one there was a carcinoma in a rather inaccessible region in the fundus of the stomach, and in another there was a carcinoma of the pancreas. In the presence of rather severe postoperative gastritis, gastroscopically confirmed, an anastomotic ulcer, usually in the form of a subacute perforated jejunal ulcer, may go unrecognized if time-honored symptoms are not evaluated carefully, as roentgenologic visualization of such lesions is frequently difficult or impossible. Or one may attribute erroneously to gastritis a disorder that is the result of a duodenal ulcer or duodenitis not recognized on roentgenoscopic examination. We have committed the same error in being slow to recognize carcinoma in the presence of hyperplastic gastritis, and conversely in submitting patients who had a tumor-simulating form of gastritis to gastric resection. I have no

apology for recommending operation in those cases in which there were persistent antral defects on roentgenologic examination, indistinguishable from carcinoma, a group which I have mentioned already. With the possible exception of the giant rugae type described by Kantor (14), such error is always excusable because of our fear of carcinoma. The final exclusion is only possible by histologic examination. One error of diagnosis, with its extenuating circumstances, is illustrated by the following case report:

Case 2. A white man aged forty-three years entered the clinic in June, 1939. Three years prior to this time, and since, he had experienced occasional epigastric fullness soon after meals. For seven months prior to admission he had complained of a burning sensation in the upper part of the epigastrium before breakfast, which would persist until relieved by this meal. During the remainder of the day he appeared to be symptom-free. Constipation also ensued. He did not experience any relief as the result of treatment for ulcer with the usual diet, antacids and feedings of milk between meals, but as a result of this he had gained 10 pounds (4.5 kg.).

Fractional analysis of gastric contents after an Ewald meal disclosed achlorhydria. On roentgenoscopic examination a defect attributed to a shallow ulcerating lesion about 1 cm. in diameter was found on the posterior wall and lesser curvature of the stomach in the upper third. Along with this there was evidence of considerable irregularity of the mucosal pattern, attributed to gastritic changes. The patient refused a gastroscopic examination.

At operation (June 16, 1939) no ulceration or tumefaction was found on exploration of the interior of the stomach through an incision in the anterior wall, but the rugae were large and hypertrophied and the general appearance was that of chronic hypertrophic gastritis. A specimen for biopsy was not taken. The abdomen was closed as an exploration. The patient was placed on a bland, high-vitamin diet and has remained well so far as his stomach is concerned. However, because of persistent constipation he again underwent examination here in August, 1940. Roentgenologic examination at this time disclosed an abnormal mucosal pattern, chiefly in the fundus of the stomach, which was attributed to hypertrophic gastritis.

PROBLEMS AWAITING SOLUTION

Apart from the problems concerned with etiology, pathogenesis, prophylaxis and causal relation to other lesions, which also have gone unsolved in large measure so far as gastric ulcer and cancer are concerned, certain puzzling aspects of possibly less formidable proportions come to the fore. The urgent necessity of investigations to verify the correlation, or lack of it, between anatomic and gastroscopic findings is exemplified by the following queries: Do changes seen by the gastroscopist always signify gastritis? Can such condition exist without being visible through the gastroscope? By what yardstick are we to determine when gastritis from a histologic standpoint is gastritis from a clinical one? To what extent does gastritis as interpreted by the gastro-

scopist differ from the gross and microscopic forms of gastritis familiar to the pathologist?

Of more important practical import are the following queries: To what extent may the clinical course of a duodenal ulcer and gastric secretory function be influenced by associated chronic gastritis, especially the hypertrophic form? What rôle does such gastritis play in postoperative recurrence and to what extent? May preoperative treatment for pre-existing gastritis prevent or minimize such recurrence? How is one to reconcile the alleged infrequency of cases of pathologically verified antral gastritis with the apparently great frequency of fundic gastritis as viewed gastroscopically? What rôle does chronic ulcerative gastritis play in the genesis of chronic gastric ulcer? Some of these questions have been answered satisfactorily in whole or in part by members of this organization and it is to be hoped that you will provide the answer to many of those that still persist.

THERAPY

Chronic gastritis, especially in its atrophic, hypertrophic and postoperative forms, is generally conceded to be refractory, and rightly so. One would expect the atrophic form to be a more or less irreversible condition. Fortunately, it does not give rise to such painful or hemorrhagic manifestations as do the other types. I am of the opinion that our pessimism may be dispelled somewhat by more intensive individualized continuous treatment at the earliest possible time, such as the more successful exponents of ulcer therapy have done. But our prognosis always must be guarded in the severe forms of gastritis, especially those following gastric resection. Prophylactic measures to forestall the disease in the majority of instances are largely a "counsel of perfection" and impracticable in the light of present knowledge.

CONCLUSIONS

The significance of chronic nonspecific gastritis as a clinical entity awaits final clarification.

Familiar types of gastritis, histologically confirmed, and observed over a period of years, are as follows: phlegmonous gastritis, acute and subacute ulcerative gastritis in association with duodenal and gastric ulcer, hemorrhagic toxic gastritis, chronic atrophic gastritis of pernicious anemia, subacute combined sclerosis, sprue, diffuse atrophic and hypertrophic gastritis secondary to disease of the circulatory, hepatic, pulmonary and incretory systems, primary chronic regional gastritis, and carcinoma simulating hypertrophic antral gastritis, postoperative diffuse and perianastomotic gastritis.

As the result of critical observation and discriminate elimination of all other intrinsic and extrinsic factors no condition other than an inflammatory disease

of the gastric mucosa, that is, gastritis, could logically explain certain forms of gastric disorder that are encountered frequently. A gastroscopic examination is indicated in every case of chronic, recurring, otherwise unexplainable dyspepsia.

Simulation of the ulcer symptom complex, or hemorrhage, or both, is a frequent manifestation of hypertrophic erosive or ulcerative gastritis, one of the most important types, clinically speaking. On the other hand, gastritis in its various forms is often symptomless.

The sources of diagnostic error in the presence of gastroscopically verified gastritis are discussed.

Our knowledge of gastritis in its various aspects is still incomplete and problems of practical import awaiting solution are discussed.

Chronic nonspecific gastritis in its various forms is generally conceded to be refractory to treatment, but intensive individualized treatment at the earliest possible moment, as in the case of gastroduodenal ulcer, should lessen our pessimism in this respect.

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HYPERTROPHIC GASTRITIS: GASTROSCOPIC AND CLINICAL STUDIES[1]

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Hypertrophic gastritis is a disease about which much confusion exists in the minds of most physicians. Since the frequent use of the flexible gastroscope, the diagnosis is now a rather common one, yet gastroscopists do not all agree on the criteria for the diagnosis. Roentgenologists frequently make a diagnosis of hypertrophic gastritis but when these patients are examined gastroscopically, the gastroscopist may find no gastritis at all or gastritis of the superficial or atrophic type. It is most encouraging, however, to realize that good correlation exists between gastroscopic and pathologic findings in the various types of gastritis (1).

DEFINITION

For the purpose of this paper hypertrophic gastritis refers to the gastroscopic diagnosis based primarily on the finding of numerous verrucous elevations in the gastric mucosa, beading or caterpillar-like appearance of the rugae, and dullness or diminished highlights in the mucosa (2). Crevasses, edema, and reddening of the crests of the rugae may be seen. Hemorrhagic areas with or without erosions are not infrequently present.

INCIDENCE

In a series of 1300 gastroscopies I have made a diagnosis of hypertrophic gastritis without other gastric or duodenal pathology in 117 cases, an incidence of 9.0 per cent. Sixty-one per cent occurred in males. The disease occurs commonly in persons from 30 to 60 years of age, rarely before 20 or after 70. The youngest patient in this series was a man of 19, the oldest a man of 77. I have also found evidence of hypertrophic gastritis in 62 cases of gastric ulcer and 51 cases of duodenal ulcer, but these are not included in this series as the symptomatology and response to treatment would be influenced by the presence of the ulcer.

SYMPTOMS

Pain. The commonest symptom of hypertrophic gastritis is *epigastric pain* which occurred in 87 cases (74 per cent). The pain is frequently described as gnawing, burning or aching. It is usually dull and may be referred to as a steady discomfort. Crampy pain is occasionally mentioned. Rarely

[1] Presented at the meeting of the American Gastroscopic Club, Atlantic City, June 7, 1942.

patients have complained of nagging, gripping, stabbing, knife-like, and violent pain, but I doubt if severe stabbing pain is ever due to hypertrophic gastritis alone. In such cases one should study the patient further for other possible sources of pain. The following table shows the frequency of the various types of pain.

Gnawing	18
Burning	11
Aching	8
Dull	8
Discomfort	8
Steady	6
Crampy	3

Pain was related to meals in 45 cases (52 per cent) and was relieved by food or soda in 71 cases (81 per cent). The similarity to ulcer pain may, therefore, be very striking. Usually it is described as non-radiating, but in 24 cases (28 per cent) radiation occurred, frequently to the back (14 cases), rarely to other parts of the abdomen or chest. Night pain was present in 18 cases (21 per cent). An attempt was made to correlate the number of patients complaining of pain with the severity or activity of the gastritis as observed gastroscopically but no relationship was found.

Other symptoms. The next commonest symptom in hypertrophic gastritis is *vomiting* which occurred in 53 cases (45 per cent). Frequently the nature of the vomiting is not stated but in 9 cases the vomitus was food recently eaten and in only 1 case was the vomitus food eaten twelve hours previously. Pyloric obstruction is thus infrequently encountered. Bile only was vomited in 8 cases, mucus only in 4 cases. Relief was obtained by induced vomiting in 5 cases. *Nausea* without vomiting was noted in 10 cases. *Gas* was observed in 48 cases (41 per cent), *sour eructations* in 19, *heartburn* in 17 cases.

Hemorrhage from gastritis has been discussed before (*3*, *4*) but should be emphasized again. In this series it occurred in 49 cases (42 per cent) with hematemesis in 31 (27 per cent). The degree of hemorrhage was considered mild in 16 cases, moderate in 14, and severe in 1 case.

TREATMENT

Unfortunately there is no specific treatment for hypertrophic gastritis. Ninety-two patients were placed on a bland diet and 26 were relieved by diet alone. Seventy-two were relieved by bland diet with or without belladonna, alkaline powders, aluminum hydroxide, hydrochloric acid, or liver therapy. In 24 cases no further information was obtainable as to the result of treatment. Nine cases were unrelieved by diet, 2 unrelieved by alkaline powders and 1 unrelieved by belladonna. Five were operated upon with relief in 3 cases

No method is 100 per cent accurate in differentiating some severe cases of hypertrophic gastritis from carcinoma. In doubtful cases surgical exploration including gastrotomy and biopsy should be performed.

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A GASTROSCOPIC STUDY OF HEALTHY INDIVIDUALS: A PRELIMINARY REPORT[1]

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Although gastroscopic literature has increased tremendously in recent years very little has been written concerning findings in healthy individuals. With few exceptions, persons subjected to gastroscopy have been patients with digestive complaints. Even though gastroscopic findings are "normal" these patients cannot be considered healthy individuals. Activated by a desire to determine the appearance of the gastric mucosa in a large number of healthy persons, the writers called for volunteers from the student body and resident staff of the University of Oregon Medical School. There has been time, so far, to complete the work in only forty individuals. Further observations will be made.

The principle reason for presenting our findings at this time is to stimulate other gastroscopists throughout the country to join with us in making a large number of examinations of healthy volunteers. The findings may be pooled at some future meeting, thus creating a background of experience from which reliable conclusions can be drawn. It should be possible to accumulate at least one thousand such observations during the next year if twenty observers will make fifty examinations each.

In order to appraise our own ability to judge the "normal" and "abnormal", it was felt desirable to compare our diagnostic results with an accepted standard. The standard selected was the experience of Dr. Schindler. His published statistics (1) of 1000 patients were compared with the findings in 500 patients of our own. To reduce errors due to inexperience the last 500 patients examined were chosen for analysis. All examinations were made with either the 45° or 50° objective. Findings in these cases are presented beside Dr. Schindler's statistics in tables 1 and 2.

It must be remembered in analyzing our figures that they cannot be considered an attempt to present accurate percentages of the frequency of gastric disease, for only *about one third of our patients with digestive complaints have been submitted to gastroscopy.* Further, one must bear in mind that only the principle gastric pathology is included in the table under the various headings e.g. gastric ulcer associated with gastritis is classified as gastric ulcer only. The lesion found gastroscopically is not always the cause of the patients chief symptoms, for instance, gastritis associated with duodenal ulcer or gallbladder disease. In many cases of atrophic gastritis bowel symptoms or

[1] Presented at the meeting of the American Gastroscopic Club, Atlantic City, June 7, 1942.

of active gastritis such as edema, abnormal mucus secretion, or inflammatory appearance.

No relationship between taking of liquor and coloring of the gastric mucosa was apparent. Four of the nine individuals taking liquor had a mucosa of average color and appearance, while in five the mucosa was highly colored, but within normal limits. The amount of liquor varied from one glass of wine to several highballs plus 1 quart of beer. There was also no relationship between the amount of liquor taken and the appearance of the mucosa. The individual taking 6 highballs and 1 quart of beer had a mucosa of average normal appearance, while the mucosa in one taking 1 glass of wine was highly colored.

Those in whom hypertrophic changes were found merit more detailed description. (a) Age 25. The mucosa was granular, highlights were de-

TABLE 3

Summary of findings

Average color and appearance:		
Fasting	26	
Rhubarb	1	
Liquor	4	
Total		31
Highly colored:		
Fasting	2	
Liquor	5	
Total		7
Hypertrophic changes		2
Total Examined		40

creased, and the rugae were segmented. Hypertrophic changes were found in the antrum and body of the stomach. There was no increase in coloring and no edema. No history of digestive disease could be elicited. (b) Age 27. The rugae were segmented and irregular. Segmental markings persisted after inflation of the stomach. No hypertrophic changes were seen between the folds. There was no edema and no increase in coloring. There was no history of digestive disturbance.

COMMENT

Of 40 healthy volunteers examined, 38 had a mucosa unquestionably within normal limits. As expected, the amount of secretion was small and did not interfere with the examination. Pigment spots and mucosal hemorrhages were not found and traumatic areas were insignificant as contrasted with the tendency to bleed on slight trauma in gastritis cases.

Two individuals classified as showing hypertrophic changes should probably not be classified as hypertrophic gastritis for they were not ill, and there was no sign of inflammatory reaction. Changes in the second case were slight but nevertheless definite. One cannot help but speculate as to the possibility of many individuals showing such changes without symptoms, and whether they may not be the result of an active process in childhood. One speculates also on the probability of such persons developing symptoms later in life under conditions predisposing to activation of the process. Surely we cannot assume from this small series that 5 per cent of healthy persons show hypertrophic changes.

On the basis of only 40 volunteers examined it would be ridiculous to draw conclusions or to do more than ask questions, hoping for a solution after a large number of volunteers have been examined by many qualified observers. In conclusion, therefore, we hope that other gastroscopists will co-operate with us in accumulating further evidence from at least one thousand individuals in various parts of the country.

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THE RELATIONSHIP OF THE CONCENTRATION OF PROTEINS IN THE SERUM TO POSTOPERATIVE GASTRIC RETENTION[1]

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Gastric retention occurring after operations on the stomach or duodenum, although not excessively common, is encountered frequently enough to be the *bête-noire* of the gastro-enterologist. Previously, basic causes for postoperative gastric retention have been ascribed to mechanical sources, such as edema in the region of the reconstruction after local operations on the duodenum, deformities of the loop of jejunum distal to a gastroenteric anastomosis due to kinking by adhesions, misplacement of the anastomosis at the time of operation and/or retraction of the stomach through the opening in the transverse mesocolon in the patient for whom a retrocolic type of anastomosis has been carred out. Such mechanical difficulties undoubtedly are serious, for relief in most instances will necessitate a secondary operation. However, after gastric surgical procedures a number of patients experience troublesome retention that may persist for variable lengths of time, from a few days to a few weeks, and then disappear spontaneously. For the distress of patients like those in this group other explanations have been suggested, such as insults to gastric tone, derangement of neurogenic mechanisms and other more vague causes.

Striking characteristics of gastric retention have been noted. Retention that appears early postoperatively; that is, within the first two or three days, is usually of much more serious consequence than retention appearing later, for in the former case it is likely that definite mechanical obstruction has occurred and that it has been present since the time of the operation. Another striking characteristic is the frequency with which a sensation of fullness, nausea, "sour stomach" or vomiting occurs on about the ninth postoperative day, a sensation which may or may not be associated with gastric retention. It might be postulated that small intramural abscesses rupture at about this time, that the absorption of catgut is a factor or that since the patient has been permitted to take gradually increasing quantities of fluid up to this point, nature finally rebels because it has not become accustomed to the new gastroenteric anastomosis.

ANTECEDENT INVESTIGATIONS

A new field of investigation recently has been explored. In 1933 Jones and Eaton reported on thirty-four patients in whom critically low concentrations

[1] Abridgment of thesis submitted by Dr. Chauncey to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of M.S. in Surgery.

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of serum proteins developed after operations. Edema was noted among twenty-six patients, twenty-one of whom had disease of the digestive tract. It was suggested that undernutrition, both preoperative and postoperative, had so lowered the values for serum proteins that edema resulted, and the possibility of this nutritional edema of the intestinal wall as a cause of poorly functioning gastro-enteric anastomosis was suggested.

In 1935 Ravdin and Rhoads said they subscribed to the hypothesis that nutritional edema of the gastro-enteric anastomosis would cause mechanical blockage, and 1937 Ravdin and associates (2, 22) presented experimental evidence in support of this view. Hypoproteinemia in dogs was induced by means of plasmapheresis and diet, and the effect on the gastric emptying time was studied. Definite delay in the gastric emptying time was found after reduction in the values for serum proteins in normal dogs as well as in animals which underwent pyloric resection. It was concluded that retention was due to narrowing of the gastro-enteric stoma, caused by the edema. The finding of low values for serum protein among patients suffering from retention after gastric surgical procedures and the considerable decrease in retention after the transfusion of blood also were reported. Obviously, many patients suffering from chronic gastric or duodenal disease are undernourished. It would be logical to assume that edema of the wall of the stomach, caused by hypoproteinemia, as well as edema caused by trauma incident to the operation (17, 33), would interfere with proper stomal function.

We noticed, however, many important differences between the observations made concerning patients reported on in the literature and observations made concerning our own patients. Edema of the wall of the stomach after or caused by hypoproteinemia would seem of necessity to be part of a generalized process, and evidence of this was noted in the reports in the literature. Generalized edema or edema of the lower extremities was a common occurrence. Free abdominal fluid and thick, edematous intestinal walls likewise were reported. In the great majority of cases in which gastric dysfunction is present postoperatively as observed in hospital services, these signs of generalized edema are lacking. It is the rare case, not the common one, in which edema of the extremities or free abdominal fluid is found. At the same time, many of our patients exhibited hypoproteinemia both with and without gastric retention. An attempt was made, therefore, to estimate the actual role played by the concentration of the serum proteins in the production of gastric retention.

NATURE OF THE PRESENT STUDY

First group. First, the concentration of serum proteins was studied in a group of seventeen normal patients; that is, patients among whom post-

operative retention did not develop. Tests were carried out at frequent intervals during the postoperative course in order to determine whether or not there was any consistent change in the values for serum protein after operation.

Second group. Second, values for serum protein were studied in a group of patients, in each of whom postoperative retention did develop. In this group of patients the effective colloidal osmotic pressure of the serum also was determined by means of semipermeable membranes. Estimations of colloidal osmotic pressures previously have been calculated mathematically from serum protein values, based on the fractional osmotic pressure due to the albumin and globulin portions—the ratio originally quoted as being 4:1 (11, 12). Adair and Robinson found this ratio to be incorrect, and Wells and his co-workers (36, 37) later suggested that "The globulin content of a given serum appears to constitute gram for gram exactly as much to the total pressure as does the albumin." The patients in the two groups studied were all patients on the surgical service of one of us (Gray), with the exceptions of two patients in the second group, whose conditions we were allowed to study by the kindness of Dr. Waltman Walters. One of these patients is reported on in case 3.

METHODS

The concentration of serum protein in a number of patients, routinely admitted to the gastro-enterologic medical services, was studied. The concentration of serum proteins was determined only after existing dehydration had been corrected, and all values, as was true in the previous two groups, were checked by hematocrit determinations.

The various laboratory tests were carried out in the following manner. All determinations of serum protein as well as the chemical investigations of the blood, done in routine manner during the postoperative course, as for example determinations of blood urea, chlorides and carbon dioxide combining power, were carried out in the biochemical laboratories of Dr. A. E. Osterberg, of the Mayo Foundation for Medical Education and Research, without whose help and kind assistance the problem could never have been carried out.

The concentration of total nitrogen was determined by the macro-Kjeldahl method and that of total proteins was calculated from the difference between the values of total nitrogen and nonprotein nitrogen. The nonprotein nitrogen was determined colorimetrically from the nesslerized digestion product of the filtrate prepared according to the method of Folin and Wu. The albumin and globulin ratio was determined by the method outlined by Todd and Sanford. Care was taken in drawing the blood to prevent any avoidable stasis.

Determinations of plasma chloride were carried out by the method of Osterberg and Schmidt, in which the Volhard principle is employed. The carbon dioxide combining capacity of the plasma was determined by the method of

Van Slyke and Cullen, as outlined by Hawk and Bergeim. Determinations of urea were carried out by the use of Van Slyke and Cullen's modification of the Marshall-urease method as outlined by Todd and Sanford. Hemoglobin and hematocrit determinations also followed the methods outlined by Todd and Sanford.

The colloid osmotic pressure of the serum was determined by the method detailed by Butt and Keys. The membranes used were fairly rigid collodion sacs. The serum was diluted with an equal volume of phosphate buffer solution of pH 7.4, the same buffer solution being used as the external fluid. The whole system was kept at 6°C. (32.0°F.) and the permeability of the membrane was checked by determinations of the content of nitrogen in both the outer and inner fluids. Determinations were made in duplicate. All the determinations of colloid osmotic pressure were carried out in the Section of Biochemistry by Dr. M. H. Power, of the Mayo Foundation, for whose help and kindness we wish also to express sincere appreciation.

In charts and graphs the daily degree of gastric retention was expressed in terms of "net retention." At times, continuous suction through an inlying tube may have been instituted for a patient, in which case the net retention was obviously the difference between the amount obtained by suction and the amount the patient took by mouth. However, at times it was slightly more difficult to estimate the amount of retention. A patient may have tolerated his diet all day, may have taken, for example, two liters of fluid, and then, later in the evening, may have begun to "feel full," and aspiration of the contents of the stomach may have showed the presence of a liter of fluid. In such an instance simple subtraction of the intake from the amount recovered by aspiration would have given negative results, but the results obviously would be wrong. An arbitrary rule was adopted which, it is recognized, is open to criticism; yet it seemed the only method that was practicable. It is this: any amount of fluid taken prior to a period of four hours before lavage was done was subtracted from the amount of retention noted, and the difference obtained was designated as "net retention." In a normally functioning stomach, postoperatively, most of the fluid taken in should pass into the intestine within a half to one hour, and certainly any fluid found after four hours, if present in large amounts, reasonably could be considered to be retained fluid. Thus, for example, if a patient tolerated a liter of fluid in the morning, took none by mouth and felt comfortable all afternoon, and in the evening was found to have 500 cc. of fluid in the stomach, the net retention was charted as being 500 cc.

TYPES OF OPERATIONS CARRIED OUT

First group. Among those patients in whom retention did not develop (seventeen in all), the following surgical procedures had been carried out:

for duodenal ulcer, partial gastrectomy for five patients, posterior gastro-enterostomy for four patients, anterior gastro-enterostomy for one patient and local excision with gastroduodenostomy for one patient; for gastric carcinoma, gastric resection for four patients; for benign gastric ulcer, gastric resection had been done for two patients.

Second group. Among the fifteen patients comprising the second group, that is, those patients among whom retention did develop, surgical procedures were carried out for nine for duodenal ulcer, for one for recurrent duodenal ulcer, for three for gastrojejunal ulcer, for one for benign gastric ulcer and for one for gastric carcinoma. The individual procedures were, for six patients, posterior gastro-enterostomy for duodenal ulcer, for one patient, anterior gastro-enterostomy for duodenal ulcer and for eight patients, partial gastric resection. In the eight instances of partial gastrectomy the operation was done in two cases for duodenal ulcer, in three cases after surgical disestablishment of a gastroenteric anastomosis that had been done for gastrojejunal ulcers, in one case for duodenal ulcer which recurred at the site at which gastroduodenostomy previously had been done, in one case for carcinoma and in one case for benign gastric ulcer.

RESULTS OF INVESTIGATIONS IN GROUP 1

It will be recalled that gastric retention did not develop among the seventeen patients in this group. Results of study of two of the patients in this group are reported in detail herein. In figures 1 and 2 are summary records of hematologic observations in these two patients and in figure 3 the composite pattern of the hematologic observations made in all cases studied in this group is seen. Determinations made in eighteen different cases appear in this figure. In seventeen of the cases in this figure the patients were "normal" (that is, gastric retention did not develop among them). In the eighteenth case the patient's condition was investigated, but unfortunately the records of other blood tests were not available. Hence, the case merely appears in the figure.

REPORT OF CASES

Case 1 (fig. 1). A woman fifty years old registered at the clinic on November 24, 1938. She had the typical symptoms of postprandial distress caused by ulcer; the symptoms had been present for twenty years. In December, 1937, the pain had become more severe, and nausea and vomiting had begun to be troublesome. In July, 1938, the patient's gallbladder and appendix had been removed elsewhere, after which the symptoms became worse and vomiting was more marked. The patient's weight had decreased from 105 to 80 pounds (48 to 36 kg.) within the year prior to her admission. Most of this loss was sustained within the two to four months prior to her admission.

Results of physical examination were essentially negative, with the exception of disclosure of marked emaciation and a visible peristaltic wave of some degree in the upper part of the abdomen. Laboratory investigations revealed the value for hemoglobin to be 11.7 gm. per 100 cc., and erythrocytes numbered 4,250,000 per cubic millimeter of blood. Gastric analysis disclosed the total acidity to be 48 units and free acid to be 42 units (method of Töpfer). A duodenal ulcer with marked obstruction was noted on roentgenologic examination.

The patient received medical preoperative treatment in the hospital, during which time fluid was administered parenterally. Gastric lavage was carried out twice a day. It was found that gastric retention preoperatively varied in amount, on the average, from 350 to 500 cc. daily.

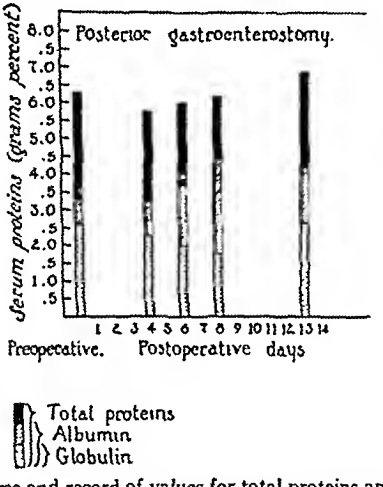

FIG. 1. Postoperative course and record of values for total proteins and the albumin and globulin fractions thereof of a woman (case 1) fifty years old who underwent a posterior type of gastro-enterostomy for pyloric obstruction that had been present for a year. Yet the concentration of proteins in the serum is within normal limits, and in spite of tremendous dilatation of the stomach as found at operation, gastric retention did not develop postoperatively.

Operation. On November 30, 1938, with the patient under the influence of general anesthesia, surgical exploration was carried out through an upper right rectus incision. A moderate number of adhesions in the upper part of the abdomen was revealed. An indurated zone was seen just distal to the pylorus. The stomach was tremendously dilated and thick-walled. Posterior gastro-enterostomy was carried out in the usual manner: the proximal loop of jejunum was approximated to the posterior wall of the stomach near the angle and anastomosis was carried diagonally to the left. Results of abdominal exploration were essentially negative except for those features just mentioned.

Postoperative course. The postoperative course was essentially normal. Gastric lavage was carried out routinely twice a day for three days, at the end of which the patient was allowed to take increasing amounts of fluid and food by mouth. She was allowed to be up on the ninth postoperative day and was dismissed from the hos-

pital on the fifteenth postoperative day. Essential laboratory data concerning the patient are seen in table 1.

Comment. The patient presented evidence of marked pyloric obstruction that had extended over a period of approximately a year. It would be expected that the effects of undernourishment, as manifested in the patient's loss of 25 pounds (11 kg.), also should bring about a condition of hypoproteinemia and thus set the stage, so to speak, for gastric retention. The preoperative value for protein in the serum was estimated after a period of days during which the fluid balance had been restored.

That the values for the concentration of protein in the serum are not "false-highs" would be indicated from the hematocrit readings (table 1), which indi-

TABLE 1

Essential laboratory data in case 1 (in which gastric retention did not develop postoperatively)

DAYS POST-OPERATIVELY	FLUID INTAKE		SALT IN PARENTERAL FLUID	GASTRIC RETENTION	URINE OUTPUT	SERUM PROTEINS			A/G RATIO	HEMATOCRIT	PROTEIN INTAKE	UREA	CHLORIDES	CO_2	HEMOGLOBIN
	Per os	Parenterally				Total	Albumin	Globulin							
	cc.	*cc.*	*grams*	*cc.*	*cc.*	*grams per 100 cc.*	*grams per 100 cc.*	*grams per 100 cc.*		*per cent*	*grams per 100 cc.*	*mg. per 100 cc.*	*mg. per 100 cc.*	*vol. per cent*	*grams per 100 cc.*
Preop.	1,500	1,000	8.5	600	1,040	6.29	3.70	2.59	1.4:1	36		20		65.5	11.7
1	0	4,000	17.0	1,350	675										
2	0	3,000	17.0	150	1,100										
3	285	2,000	8.5	0	2,300						10	16	561	57.9	
4	1,040	1,000	8.5	100	2,400	5.58	3.33	2.25	1.47:1	36	18	Progressive diet			
5	1,025	1,000	0	0	1,500						36	Progressive diet			
6	1,700	0	0	0	1,400	6.0	4.03	1.97	2.04:1	37	45	Progressive diet			
7	1,950	0	0	0	1,100						51	Progressive diet			
8	2,700	0	0	0	700	6.19	4.41	1.78	2.47:1	33	58	Progressive diet			
9	2,700	0	0	0	1,000						60	Progressive diet			
10	2,400	0	0	0	1,400						72	Progressive diet			
11	2,000	0	0	0	1,050						72	Progressive diet			
12	1,960	0	0	0	815						72	Progressive diet			
13	2,300	0	0	0	NC	6.87	4.21	2.66	1.58:1		80	Progressive diet			

cated, as a matter of fact, that not only had dehydration been corrected but also that, if anything, hemodilution had occurred to a limited extent. The daily output of urine, which was consistently near one liter, also would indicate that dehydration had not been present. Even after a year of pyloric obstruction, the concentration of protein in the serum was within normal limits. After operation, a decrease in the concentration of both albumin and globulin occurred coincidentally, the albumin regenerating, surprisingly enough, more rapidly than the globulin, the concentration of which (globulin) later continued to decrease until at least the eighth day (table 1). By the eighth day the concentration of total proteins returned to about the value that had been noted at the patient's admission; it was more than the value at admission on

the thirteenth day, and at no time were the so-called critical edema values reached.

It is noteworthy that in spite of the tremendous dilatation of the stomach found at both roentgenologic examination and operation, postoperative retention did not develop.

Case 2 (fig. 2). A man, forty-four years old, originally had registered at the clinic on January 4, 1913. At that time, at the age of eighteen years, he had given a history of epigastric distress, with seasonal variations, that had extended over ten years. This postprandial pain could be relieved by the taking of food or, frequently, by induced vomiting.

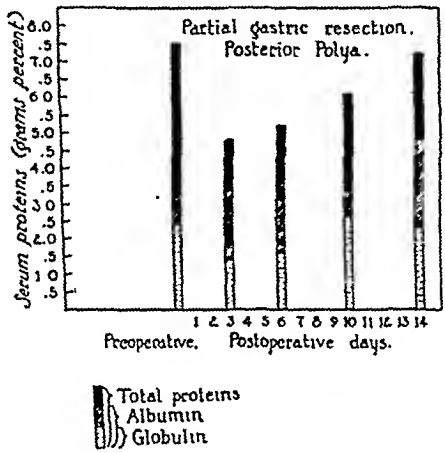

FIG. 2. Postoperative course and record of values for total proteins and the albumin and globulin fractions thereof of a man (case 2) forty-four years old who underwent, in 1913, an antecolic type of gastro-enteric anastomosis and appendectomy, in 1926, side-to-side gastroduodenostomy and surgical disestablishment of the previous gastro-enteric anastomosis, and in 1938, partial gastric resection and re-establishment of gastro-intestinal continuity by means of a posterior Polya type of anastomosis. After dehydration had been corrected the concentrations of protein, both total and fractions, thereof, were normal, despite the fact that marked gastric retention and vomiting had been present for two years.

Gastric analysis disclosed a total acidity of 48 units and free acid of 40 units (method of Töpfer). Because the clinical impression was that the appendix was implicated, in addition to the presence of duodenal ulcer, the patient underwent surgical exploration. A chronic, adherent, duodenal ulcer was found and performance of an antecolic type of gastro-enteric anastomosis was necessitated by a very short transverse mesocolon. Appendectomy also was done.

The patient experienced some, but not complete, relief. A few years later the periodic, seasonal type of distress recurred, with some change in the character of the pain. Pain was noted to occur more to the left and lower in the abdomen than had been the case previously. He returned to the clinic in 1926, at which time he was found (at roentgenologic examination) to have a perforating gastrojejunal ulcer. The pylorus was patent. The gastro-enteric anastomosis was disestablished surgi-

cally and, because of the pliability of the pylorus, side-to-side gastroduodenostomy was carried out.

Within six months the symptoms recurred. They persisted in spite of the patient's adherence to a medical regime. A year later the patient experienced hemorrhage for the first time. Hemorrhage recurred and, in all, four episodes of hemorrhage had occurred by 1929. During the two years previous to the patient's last admission, nausea had been present every day, and frequent vomiting was the rule. He had marked retention when he was first examined at the clinic. The amount was 1,670 cc. on one occasion. For more than a week the patient was treated medically in the hospital preparatory to surgical intervention. The amount of daily gastric retention varied from 800 to 1,750 cc. Solutions of glucose and sodium chloride were administered intravenously.

Roentgenologic investigation disclosed a recurring duodenal ulcer with marked obstruction, and gastric analysis showed the total acidity to be 64 units and free acid, 58 units (method of Töpfer). Preoperative laboratory investigation of the concentration of protein in the serum was carried out after dehydration had been corrected.

Operation. On December 7, 1938, with the patient under the influence of general anesthesia, exposure was achieved through a former incision in the midline. A tremendous mass of adhesions, particularly in the upper part of the abdomen, was found. A recurrent ulcer was evident in the region in which the previous gastroduodenostomy had been carried out, and almost complete obstruction was found. The stomach was tremendously dilated, to almost three times normal size, and was markedly thick walled. Gastric resection was done in which slightly more than half the stomach was removed, and gastro-intestinal continuity was re-established by performance of a posterior Polya type of anastomosis.

During operation 500 cc. of whole citrated blood was transfused to the patient and 500 cc. of a 6 per cent solution of acacia was administered. Twenty-four hours after the operation 500 cc. of dark, bloody retained material was recovered by aspiration. It is impossible to estimate just how much the transfused blood affected the subsequent determinations of protein in the serum (table 2 and fig. 2), but the net result probably was not great.

Postoperative course. The postoperative course was uneventful; the patient was allowed to be up on the ninth day and was dismissed from the hospital on the fifteenth day. Laboratory data are seen in table 2.

Comment. For a number of reasons the condition of this patient was one of the most interesting of those studied. In spite of the fact that marked retention and daily vomiting had been present for two years, the concentration of serum proteins, both total and fractional estimations, was normal when it was estimated after dehydration had been corrected. Not only low normal values but also relatively high normal values were obtained. It can be stated with confidence that the regenerative mechanism of serum proteins was not interfered with appreciably. In spite of the normal concentration of serum proteins, higher in this case than in many of the other cases, plus the trans-

fusion of blood on the day of operation, the decrease in the concentration of protein in the serum after operation was marked. The albumin fraction contributed slightly more to this decrease than did the globulin fraction. Subsequently, regeneration of the two fractions occurred in an unpredictable manner. Both the albumin and globulin concentrations gradually increased until the tenth postoperative day, after which the globulin fraction decreased, whereas there continued to be a marked increase in the albumin concentration (table 2).

This case constitutes an interesting example of a group of cases which would lead to the conclusion that no prediction as to the concentration of protein in

TABLE 2

Essential laboratory data in case 2 (in which gastric retention did not develop postoperatively)

DAYS POSTOPERATIVELY	FLUID INTAKE		SALT IN PARENTERAL FLUID	URINE OUTPUT	GASTRIC RETENTION	SERUM PROTEINS			A/G RATIO	HEMATOCRIT	PROTEIN INTAKE	UREA	CHLORIDES	CO_2	HEMOGLOBIN
	Per os	Parenterally				Total	Albumin	Globulin							
	cc.	*cc.*	*grams*	*cc.*	*cc.*	*grams per 100 cc.*	*grams per 100 cc.*	*grams per 100 cc.*		*per cent*	*grams per 100 cc.*	*mg. per 100 cc.*	*mg. per 100 cc.*	*vol. per cent*	*grams per 100 cc.*
Preop.	1,600	1,000	8.5	NS	1,300	7.52	5.07	2.45	2.07:1	46		36	571	54.1	14.6
1	0	4,000	17.0	360+	0										
2	0	2,000	17.0	965+	860										
3	300	2,000	17.0	1,000	360	4.88	3.42	1.46	2.34:1	36		20	594	41.2	
4	605	2,000	0	1,150	10						Fluid intake				
5	1,030	1,000	8.5	1,700	0										
6	1,280	0	0	850	0	5.27	3.65	1.62	2.25:1		Progressive diet				
7	1,800	0	0	450	0						26	Progressive diet			
8	2,150	0	0	650	0						45	Progressive diet			
9	2,050	0	0	1,200	0						51	Progressive diet			
10	2,250	0	0	1,300	0	6.14	3.46	2.68	1.21:1		58	Progressive diet			
11	2,500	0	0	1,500	0						60	Progressive diet			
12	2,260	0	0	1,150	0						60	Progressive diet			
13	1,900	0	0	NS	0						72	Progressive diet			
14	2,400	0	0	NS	0	7.26	4.88	2.38	2.05:1		72	Progressive diet			

the serum can be made with any degree of accuracy on the basis of the presence in the patient's history of the factors of obstruction and vomiting.

Other cases in group 1. The most surprising observation was the relatively small decline of the total concentration of proteins, even in the presence of marked obstruction. The normal concentration of protein in the serum as given by Furey on the basis of work carried out in the biochemical laboratory of Dr. A. E. Osterberg in the Mayo Foundation is: for total proteins, an average of 7.36, with a range of from 6.2 to 8.1; for albumin, an average of 4.92, with a range of from 4.1 to 5.8; and for globulin, an average of 2.40, with a range of from 1.7 to 3.5, all the aforementioned values being expressed in grams per 100 cc. of serum. The average values found in these se
were: for total protein, 6.64, with a range of from 5.87 to 7.76·

4.56, with a range of 3.55 to 5.2; and for globulin, 2.08, with a range of 1.34 to 2.68, gm. per 100 cc. The average values thus were indluded within the normal range, although they were slightly lower than the average values that are obtained among normal people. An individual value that was very striking was found in one case. The patient had had obstructive vomiting for six weeks, and at the patient's admission the concentration of total proteins was found to be 4.93 gm. per 100 cc. Of this, albumin accounted for 4.19 gm. and globulin for only 0.74 gm. By use of the normogram published by Wells, Youmans and Miller, which was found to agree within limits of 20 to 30 mm. of water with observed colloid osmotic pressures determined in the cases in which retention was present, the colloid osmotic pressure would be about 230 mm. of water; that is, reasonably well in excess of the "critical edema level." Neither gastric retention nor edema developed postoperatively in this patient.

The values shown in figure 3 proved to be of interest. A marked decrease in the concentration of protein in the serum occurred during the first few days postoperatively. On about the fifth to sixth day the decrease in concentration ceased, and a progressive and steady increase began. This increase usually began to be noticeable before any adequate amount of protein was taken in. It may be that a small intake of protein serves, nevertheless, as a stimulus to regeneration.

Fluctuations in the two protein fractions displayed no consistency. A decrease in the concentration of albumin relatively greater than the decrease in the concentration of globulin frequently was seen, and yet in three cases the decrease in the concentration of total proteins was due solely to a decrease in the globulin fraction, an actual increase in the albumin fraction having been noticed. Most frequently, the concentration of albumin displayed a greater tendency to fluctuate than did the concentration of globulin.

Of much greater interest, however, were the relatively low values obtained between the third and the seventh postoperative days. A concentration of total protein of less than 5.5 gm. per 100 cc. was found thirteen times; a concentration of albumin of between 3.0 and 3.5 gm. per 100 cc. was found eleven times. As will be elaborated later, these values are of note in view of the fact that all the patients concerned had a normal postoperative course. Frequently, cases are reported in the literature in which a concentration of protein of, say, 5.5 gm. per 100 cc. is noted on the sixth postoperative day. The existing gastric retention is thought to be related to this concentration. We desire only to emphasize herein the frequent finding of similar values occurring at this period when the postoperative course has been normal. Interesting, for the same reason, is the general return of the concentration of protein in the serum to preoperative values or even more than those values, by the tenth to the twelfth postoperative day. This is significant in view of the

fact that gastric retention first appears in the majority of patients who have experienced a normal postoperative course during this period of the first nine to twelve days.

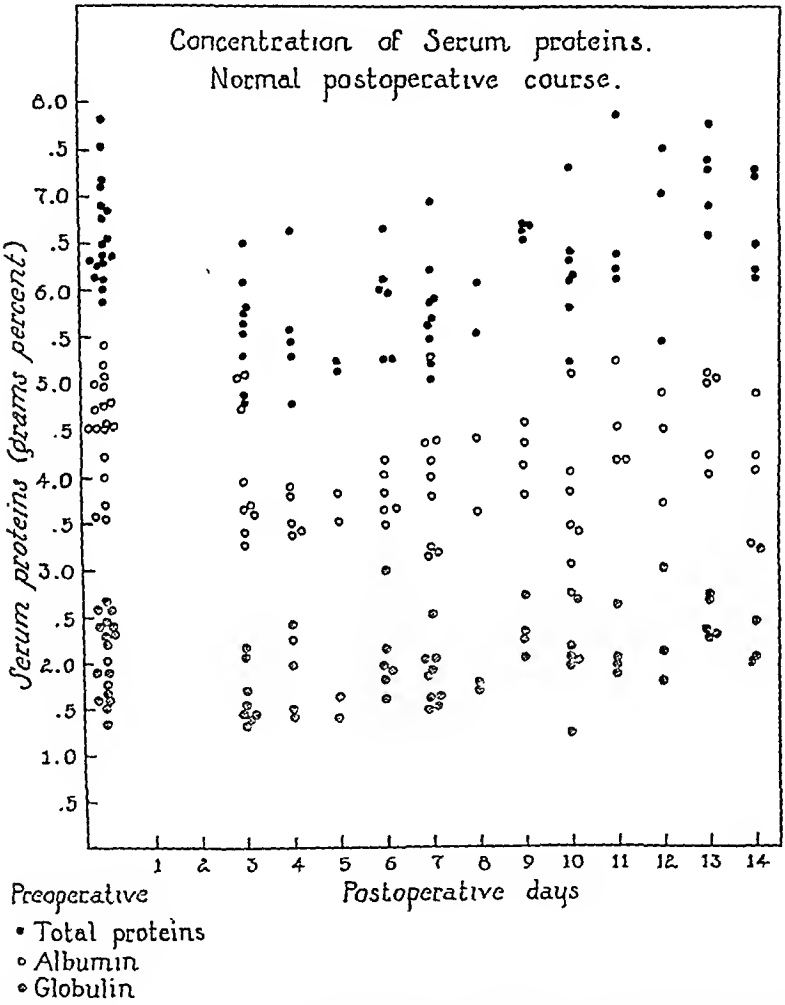

FIG. 3. [illegible] preoperative and postoperative values for total proteins and the albumin [illegible] in eighteen cases in which gastric retention did not develop postoperatively. [illegible] cases figure in this group in the present study, as is explained in the text.

RESULTS OF INVESTIGATIONS IN GROUP 2

Group 2, it will be recalled, was the group in which gastric retention did develop postoperatively. Two of the total of fifteen cases studied will be reported herein.

REPORT OF CASES

Case 3 (fig. 4). A man fifty-four years old first registered at the clinic on August 8, 1921, at which time he gave a history of having had a duodenal ulcer for five years. Roentgenologic investigation at the time of admission disclosed a duodenal ulcer, with gastric retention. Since a chronic duodenal ulcer with obstruction was present in a patient who was more than fifty years old, posterior gastro-enterostomy was carried out. At the time of operation the stomach was found to be dilated, and considerable obstruction was observed. After this operation the patient was relieved of all symptoms for a period of four years, at the end of which, after a period

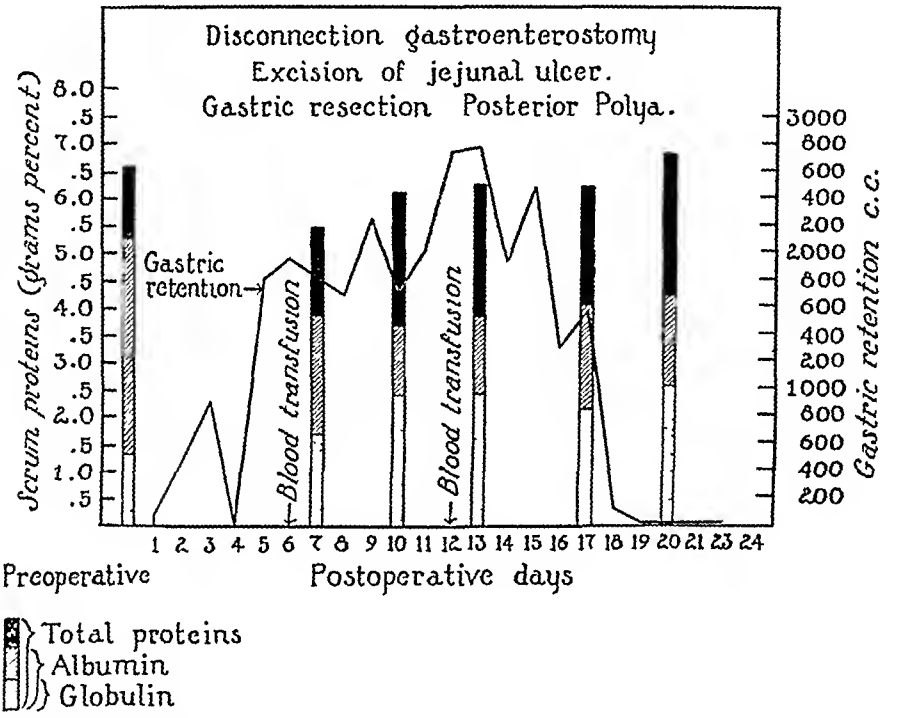

FIG. 4. Postoperative course and record of values for total proteins and the albumin and globulin fractions thereof of a man (case 3) fifty-four years old who underwent a posterior type of gastro-enterostomy in 1921 and partial gastrectomy and re-establishment of gastro-intestinal continuity by means of a posterior Polya type of anastomosis in 1939. Gastric retention increased in degree in this case after the final operation, but contrary to all expectations, the concentration of proteins in the serum also increased.

of dietary indiscretion and financial worry, periodic epigastric distress recurred. The symptoms were relieved and the patient was maintained on a strict medical regime from that time until 1934. There were, however, mild periodic recurrent attacks associated with periods of hard work and excessive worry. The patient returned in 1934, at which time it was thought advisable to continue the so-called ulcer type of treatment, with antispasmodic and sedative agents. This was done, and no severs attacks of pain occurred, but mild periodic distress was still present. Six monthe before the patient's last admission (January 27, 1939) symptoms had become more severe and relief obtained by the taking of food was less marked. During this period

pain at night was first noticed, and the pain could not be relieved by the taking of alkalies. At admission the patient appeared to be somewhat emaciated, and had recently lost 25 pounds (11 kg.). Results of physical examination otherwise were not remarkable.

Roentgenologic investigation of the upper part of the gastro-intestinal tract revealed a duodenal deformity caused by an old ulcer, with some obstruction at the pylorus, and the stoma created at the time of gastro-enterostomy in 1921 was found to be completely closed. Gastric analysis at this time revealed the total acidity to be 40 units and free hydrochloric acid to be 30 units (method of Töpfer). The clinical impression was that a reactivated duodenal ulcer, with obstruction, was present, and surgical intervention seemed advisable. The patient was maintained in the hospital on medical management, during which time fluids were administered intravenously and the daily gastric retention varied in amount from 250 to 300 cc.

Operation. On February 4, 1939, with the patient under the influence of general anesthesia, the abdomen was explored. Exposure made through the old upper right rectus incision revealed a chronic duodenal ulcer with considerable scarring, and blockage of the outlet of the stomach. The region of the previous gastro-enteric anastomosis was examined. A small jejunal ulcer was noted, with a moderate inflammatory reaction. The gastro-enteric anastomosis was disestablished and the jejunal ulcer was excised. Partial gastrectomy was carried out: slightly more than half of the stomach was removed and gastrointestinal continuity was re-established by means of a posterior Polya type of anastomosis.

Postoperative course. Persisting gastric retention appeared early in the post-operative course (fig. 4), the amount of material retained increased largely between the fourth and sixth postoperative days, and thereafter varied between 2,700 and 1,300 cc. After the fifteenth postoperative day a marked progressive and constant decline in the degree of retention occurred and retention itself disappeared on the nineteenth day. Five hundred cubic centimeters of whole, citrated blood was transfused to the patient on the sixth postoperative day and 350 cc. was transfused on the twelfth postoperative day (fig. 4). Nasal suction was instituted on the fifth post-operative day and was continued until the thirteenth postoperative day, at which time it was discontinued and lavage of the stomach was carried out twice daily. The patient was dismissed from the hospital on the twenty-third postoperative day. At that time he was taking an adequate amount of fluid and food by mouth.

The essential laboratory data in this case appear in table 3.

Comment. Estimation of the concentration of protein in the serum throughout the postoperative convalescence of this patient proved interesting. In spite of the inadequate amount of the intake of protein of the patient previous to his admission, the concentration of total proteins was found to be within normal limits and the concentration of albumin was within high normal limits. Subsequent to operation, from the seventh to the thirteenth postoperative day, at the end of which there occurred a progressive increase in the degree of daily

gastric retention, the concentration of serum protein also was increasing, a phenomenon which was just the opposite of the expected result. The colloid osmotic pressure was well in excess of critical edema limits (160 to 200 mm. of water). It is likewise interesting to note that, during the period in which blood was transfused to the patient, in spite of a steady increase in the concentration of protein in the serum, the degree of gastric retention also increased and, indeed, the concentration of protein during the period of the maximal

TABLE 3

Essential laboratory data in case 3 (in which gastric retention did develop postoperatively)

DAYS POSTOPERATIVELY	FLUID INTAKE		SALT IN PARENTERAL FLUID	GASTRIC RETENTION	URINE OUTPUT	SERUM PROTEINS			A/G RATIO	HEMATOCRIT	C.O.P.	UREA	CHLORIDES	CO_2	HEMOGLOBIN	PROTEIN INTAKE
	Per os	Parenterally				Total	Albumin	Globulin								
	cc.	*cc.*	*grams*	*cc.*	*cc.*	*grams per 100 cc.*	*grams per 100 cc.*	*grams per 100 cc.*		*per cent*	*mm. water*	*mg. per 100 cc.*	*mg. per 100 cc.*	*vol. per cent*	*grams per 100 cc.*	*grams per 100 cc.*
Preop.	2,000	1,000	8.5	350	BR	6.59	5.28	1.31	4.03:1	53		30			15.3	
1	0	4,000	17.0	75	400+											
2	0	3,000	25.5	480	1,325											
3	360	3,000	25.5	900	600							32	578	48.5		
4	395	3,000	25.5	0	1,250											
5	0	3,000	25.5	1,830	1,350							Nasal suction				
6	0	3,000*	25.5	1,980	1,400							26	623	53.2	19.6	
7	0	3,000	25.5	1,830	1,250	5.58	3.87	1.71	2.6:1	44	254					
8	0	2,800	23.8	1,700	865							24	578	49.5		
9	0	2,400	18.7	2,265	750+											
10	0	3,000	17.0	1,710	1,000	6.11	3.69	2.42	1.52:1	45	237	30	495	49.5		
11	0	3,000	25.5	2,050	600+											
12	0	3,000*	17.0	2,750	900											
13	0	3,000	27.4	2,785	1,050	6.25	3.84	2.41	1.58:1	42	302	Nasal suction discontinued				
14	885	3,000	29.1	1,925	550+							22	511	68.3		
15	1,320	3,000	29.1	2,485	1,350											
16	1,630	3,000	27.4	1,330	BR											
17	1,730	3,000	21.3	1,570	BR	6.20	4.05	2.15	1.81:1	39	267	10	475	69.2		
18	1,740	1,500	8.5	120	BR											
19	1,890	1,500	8.5	0	BR											
20	1,425	1,000	8.5	0	BR	6.81	4.28	2.53	1.69:1	44	274	Progressive diet				18
21	1,580	0	0	0	BR							Progressive diet				26
22	1,270	0	0	0	BR							Progressive diet				45

* 500 cc. of blood transfused on the sixth postoperative day; 350 cc. transfused on the twelfth postoperative day.

degree of gastric retention was essentially the same as that noted during the period in which retention diminished and disappeared. It would seem reasonable to conclude that, at least in this case, the effect of colloid osmotic pressure of the serum proteins, measured either directly or measured indirectly (by means of protein concentrations), played no part in determining the onset, the degree of, or the disappearance of, gastric retention.

Case 4 (fig. 5). A man fifty-four years old first registered at the clinic on May 4, 1938, at which time he presented a three-year history of epigastric distress. Shortly

after the onset of the distress, vomiting had become such a marked feature that the patient had carried out gastric lavage daily. As a complicating feature the patient presented a history of renal colic of recent origin. Roentgenologic investigation at that time revealed a duodenal ulcer with obstruction, and multiple stones were seen in the left kidney. Gastric analysis disclosed the total acidity to be 74 units and free hydrochloric acid to be 66 units (method of Töpfer). On May 10, 1938, posterior gastro-enterostomy was performed. A chronic duodenal ulcer was found just distal to the pylorus, with moderate induration and obvious obstruction. The stomach was found to be one and a half times normal size and moderately thick walled. Pre-

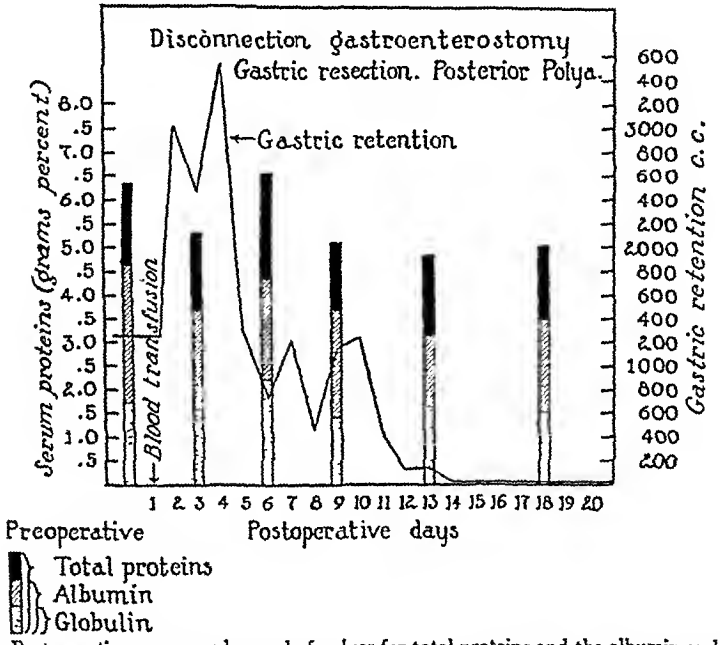

FIG. 5. Postoperative course and record of values for total proteins and the albumin and globulin fractions thereof of a man (case 4) fifty-four years old who underwent a posterior type of gastro-enterostomy in 1938, surgical enlargement of the contracted stoma in 1938, and partial gastrectomy and re-establishment of gastro-intestinal continuity by means of a posterior Polya type of gastro-anastomosis in 1938. Surprisingly enough, postoperative gastric retention, which if it is caused by hypoproteinemia should have been most severe on the thirteenth day, when the lowest value for serum protein was obtained, actually disappeared on that day.

vious to this operation, while the patient was maintained by medical management in the hospital, daily gastric retention had varied in amount between 400 and 1,300 cc. The postoperative course was complicated by the appearance of gastric retention which lasted until the eleventh postoperative day, and the patient was dismissed from the hospital a few days later.

The patient returned to the clinic on July 9, 1938. He had been well after the last operation until a week previous to his admission, when he again experienced some degree of obstruction to the emptying of his stomach, and marked vomiting. Four days previous to his admission, severe renal colic on the left had occurred. The patient was sent directly to the hospital and received fluids intravenously. Gastric

lavage was carried out daily. Roentgenologic investigation of the stomach disclosed considerable dilatation with some degree of pyloric obstruction and a malfunctioning gastro-enteric anastomosis. It was felt that although it was possible that the renal colic had caused a certain portion of the vomiting experienced prior to his admission, the gastric situation demanded correction first. Consequently, with the patient under the influence of spinal anesthesia, laparotomy was carried out on August 14.

The gastrojejunal stoma was found to have contracted to about 2 cm. in diameter. The stoma was enlarged surgically. Gastric resection at the time seemed advisable, but the patient was in no condition to endure such a procedure and it was thought that, by enlargement of the stoma, means might be provided by which the patient could attain better physical condition. The postoperative course was again marred by gastric retention which, however, cleared by the thirteenth day. The patient was dismissed again from the hospital.

The patient's last admission was on December 11, 1938. He had gained 60 pounds (27 kg.) and had been entirely free from symptoms until two weeks prior to his registration when, on resumption of his office duties and under the strain of overwork and dietary indiscretions, generalized abdominal pain had recurred, and with it, an obstructive type of vomiting. Roentgenologic investigation disclosed a malfunctioning gastro-enteric anastomosis and no barium was seen to pass through the pylorus. The severity of the pain seemed to indicate the presence of a jejunal ulcer; consequently surgical intervention was advisable.

Operation. On December 15, with the patient under the influence of general anesthesia, surgical exploration was done. A large gastrojejunal ulcer was found on the posterior wall at the junction of the proximal loop of the jejunum and the stomach. It penetrated the transverse mesocolon and fixed the proximal loop of jejunum. The ulcer was about 2.5 to 4 cm. in diameter. A second ulcer situated on the anterior wall of the anastomosis was approximately 1.5 cm. in diameter. There was a tremendous amount of edema and infiltration in the vicinity of these ulcers. Partial gastrectomy was done, in which approximately two-thirds of the stomach was removed. Gastro-intestinal continuity was re-established by means of a posterior Polya anastomosis.

Postoperative course. Immediately after the operation 500 cc. of whole citrated blood was transfused to the patient. Retention occurred after the operation and endured until the fourteenth postoperative day. On the fifth postoperative day a marked decline in the reaction was noticeable, and between the fifth and tenth postoperative days retention varied in amount from 600 to 1,200 cc. daily. A second marked decline in retention was noticed after the eleventh postoperative day, and retention finally cleared on the fourteenth postoperative day. The patient was dismissed on the nineteenth postoperative day, at which time an adequate dietary intake was being tolerated. Essential laboratory data concerning this patient will be found in table 4.

Comment. The preoperative concentration of protein in the serum was within normal limits in this case, as would be expected by the facts that the

patient had gained 60 pounds (27 kg.) and malnourishment had been present for only two weeks. The decline in the concentration of proteins noticed on the third day (table 4) was of the same order as that observed of normal patients. The subsequent course was one of the most interesting that we observed. This patient was one of the two in the series in whom clinical edema developed. From the sixth until the thirteenth postoperative day there was a steady decline in the concentration of proteins (table 4), during the same period in which the degree of gastric retention was decreasing. The lowest value for serum protein, 4.86 gm. per 100 cc., was recorded on the thirteenth

TABLE 4

Essential laboratory data in case 4 (in which gastric retention did develop postoperatively)

DAYS POSTOPERATIVELY	FLUID INTAKE		SALT IN PARENTERAL FLUID	GASTRIC RETENTION	URINE OUTPUT	SERUM PROTEINS			A/G RATIO	HEMATOCRIT	C.O.P.	UREA	CHLORIDES	CO_2	HEMOGLOBIN	PROTEIN INTAKE
	Per os	Parenterally				Total	Albumin	Globulin								
	cc.	cc.	grams	cc.	cc.	grams per 100 cc.	grams per 100 cc.	grams per 100 cc.		per cent	mm. water	mg. per 100 cc.	mg. per 100 cc.	vol. per cent	grams per 100 cc.	grams per 100 cc.
Preop	1,150	1,000	8.5	1,250	BR	6.36	4.65	1.71	2.7:1	46		22	522	63.6	15.8	
1	0	4,850*	24.9	0	450	Blood transfused during operation										
2	0	4,150	17.0	3,050	1,175											
3	0	3,550	29.7	2,460	1,725	5.30	3.70	1.60	2.3:1			30	561	52.2	12.3	
4	0	3,475	17.0	3,510	2,050											
5	0	2,000	17.0	1,300	850											
6	820	2,000	17.0	730	1,025	6.57	4.36	2.21	1.9:1		253	27	538	65.5	No edema	
7	1,640	2,000	17.0	1,220	850											
8	1,005	2,000	17.0	450	1,275											
9	765	1,000	8.0	1,155	900	5.12	3.70	1.42	2.5:1							
10	895	2,000	17.0	1,250	1,425											
11	1,095	2,000	17.0	400	1,375						Dry diet					
12	1,480	2,000	17.0	130	1,350						Progressive diet					10
13	1,080	1,000	8.5	135	1,300	4.86	3.17	1.69	1.9:1		160					26
14	1,575	1,000	8.5	0	1,875											60
15	1,550	1,000	8.5	0	970							14	594	60.7	8.7	72
16	1,935	0	0	0	BR											72
17	2,370	0	0	0	BR											72
18	2,425	0	0	0	BR	5.06	3.50	1.56	2.2:1							80
19	2,050	0	0	0	BR											80

* 500 cc. of blood transfused day of operation.

postoperative day (table 4). Coincidentally, the colloidal osmotic pressure was within critical edema limits: 160 mm. of water. Yet, at that time, gastric retention disappeared, at the very time at which, if it had existed on the basis of hypoproteinemia, it should have reached a maximum. The effect of salt administered parenterally in the production of edema, demonstrated so clearly in the laboratory (7, 8, 18, 19, 35), found clinical application here. During the early postoperative course, when the patient was receiving 30 gm. of sodium chloride, slight but definite clinical edema was present. Later, with the administration of less salt, edema slowly disappeared, although the concentration of proteins became less.

COMMENT

From the time that Starling originally drew attention to the role played by the serum proteins in the phenomena of absorption, much evidence has accumulated in support of that conception. There has been shown to be a gradual decline in the hydrostatic pressure in the capillary loops from the proximal to the distal portions. The predominance of hydrostatic pressure over colloid osmotic pressure in the proximal loop, then, would tend to force water and salt through the capillary wall and into the tissues; as the forces become more equal the interchange would become progressively less marked in the distal portions, the colloid osmotic pressure being greater than the hydrostatic pressure, and fluid would be reabsorbed. If this delicate mechanism is distributed by a lowered colloidal osmotic pressure, with consequently greater filtration than absorption, edema would result, other factors previously discussed being equal. The application of this simple concept to the production of postoperative gastric retention is at once interesting and attractive.

In various conditions a basis for such a belief would seem to be present. In starvation, in endemic malnourishment, in all experiments with plasmapheresis, lowered concentrations of proteins in the serum almost invariably lead to edema. In 1933 the report of Jones and Eaton, previously referred to, drew attention to edema in postoperative cases. This report was of tremendous importance in view of the fact that it centered attention on the problem and stimulated investigative work. The conclusions reached by Ravdin and his co-workers likewise were of tremendous interest.

It is expected that many patients suffering from chronic disease of the upper part of the gastro-intestinal tract will exhibit malnourishment in a like manner. It was surprising to observe that relatively minor degrees of hypoproteinemia were found even in the presence of longstanding duodenal obstruction. Even more surprising was the lack of development of postoperative gastric retention among those few patients who did have marked hypoproteinemia preoperatively. This would seem to bear out clinically the experimentally adduced contention that there is a marked power of protein regeneration, a contention that has been stressed by so many investigators (3, 14, 18, 22, 23, 24, 27, 31).

Just as surprising were the results of observations among patients in whom gastric retention did develop postoperatively. If postoperative gastric retention were due to malfunctioning of the stoma caused by edema of the stomal tissues, such edema having been caused by the lowered serum colloidal osmotic pressure engendered by a state of hypoproteinemia, then one should reasonably expect that retention would occur when the colloidal osmotic pressure decreased to the "critical edema level." Furthermore, one would expect

that the stomal edema would be part of a general picture; that is, that subcutaneous edema also would be present. Last, one would expect that, as the concentration of proteins in the serum increased and as the colloidal osmotic pressure of the serum surpassed the "critical edema level," gastric retention should diminish and disappear. These expectations had indeed been fulfilled in the observations of Jones and Eaton, and in the experimental and clinical investigations of Ravdin and his co-workers. In the present series, however, there were striking variations from these anticipated results.

The colloidal osmotic pressure of the serum proteins has been estimated by many workers (5, 6, 20, 25, 29, 30). The results expressed in millimeters of water vary slightly according to the conditions under which the determinations are carried out. Butt and Keys and Kerkhof had established the "critical edema level" as being approximately 200 mm. of water, and they used the same technic as was used in our study. Fortunately, Goudsmit (11), using a technic that was identical to our own, carried on concurrent investigations in cases of nephritis with edema, and found the "critical edema level" to be about 160 mm. of water.

In view of this research, the following results are of interest. In case 3, the serum colloidal osmotic pressure was 254 mm. of water at the time that gastric retention developed (table 3). This was well in excess of the edema level, in spite of the fact that the concentration of protein in the serum was 5.56 gm. per 100 cc. In another case gastric retention developed and very markedly increased between the tenth and the twelfth days, a period during which the colloid osmotic pressure was 251 mm. of water. Retention was still present in amounts greater than 2,000 cc. daily when the colloid osmotic pressure of the serum was 234 mm. of water. Still another case served as an even more striking example. On the twelfth day gastric retention suddenly developed, reaching a maximum on the sixteenth day and disappearing on the nineteenth day. On the morning of the thirteenth day the values for proteins in the serum were within normal limits and the colloid osmotic pressure of the serum was 285 mm. of water (85 mm. in excess of the "edema level").

Different results might be expected in the presence of demonstrable edema. In the present series this occurred only twice (one instance of it is described in the report of case 4). In both these cases, the colloidal osmotic pressure was well below 200 mm. of water, yet in each case gastric retention was diminishing at the time edema was noted, and it disappeared shortly thereafter. Such observations are in agreement with those of Snell (32, 33), who observed patients who had postoperative edema caused by hypoproteinemia but did not have gastric retention.

The fluctuations in the amount of material retained daily should be interesting. If one were to postulate that if retention ought to become greater

as the concentration of protein in the serum becomes reduced or, that retention ought to become less as the concentration of serum proteins increases, a relationship in the order of cause and effect might thereby be established. Not only would the amount of edema about the stoma be expected to be greater in the presence of lower concentrations of protein in the serum, but, also, it would be expected that less absorption would take place in the gastro-intestinal tract. Since it has been suggested that a relationship exists between the absorbing force and the concentration of protein, it would be expected that more fluid would be available from the intestinal secretions themselves.

Once again, however, the results found were at variance with those expected. In case 4 there was a marked and steady decrease in the amount of daily retention which practically paralleled the decrease in the concentration of serum protein (fig. 5 and table 4) and decrease in colloidal osmotic pressure. When the osmotic pressure had reached the "critical edema level" of 160 mm. of water, when the concentration of protein in the serum was 4.86 gm. per 100 cc. (table 4) and when subcutaneous edema became manifest clinically, gastric retention finally disappeared (fig. 5)!

One other factor remains to be mentioned. One of the most striking features of prolonged gastric retention was the rapidity with which such retention disappeared after the institution of jejunal feedings. At first thought this would seem to be due to the expected increase in the concentration of protein in the serum resulting from the jejunal feedings. However, although the same effect was found in three cases in which jejunostomy was done for the relief of retention, in each an unexpected result was noted. In two of these cases the concentration of protein in the serum increased subsequent to the institution of jejunal feedings, then later diminshed, and it was during the period of decrease in the concentration of the protein that the gastric retention diminished. In one of the aforementioned two cases there was no immediate increase in the concentration of serum protein, yet gastric retention diminished and disappeared. It would seem more likely, therefore, that other factors are responsible for the dramatic improvement observed after the performance of jejunostomy in cases of severe retention. It is impossible to state what these factors are, but one cannot help speculating that such factors as the restoration of normal intestinal gradient, and the stimulus of peristaltic waves that would follow the introduction of food in the distal limb of the jejunum, may play major parts.

In this series of patients it was thought beforehand that hypoproteinemia might be incriminated as the cause of the postoperative gastric retention. Hypoproteinemia did occur, but on the basis of the results we have set forth it would not seem to be the basic cause of postoperative gastric retention. Hy-

poproteinemia occurred among patients in whom postoperative gastric retention did not develop. It disappeared and the concentration of protein in the serum returned to normal in the period in which retention often occurred.

Although it is not to be denied that should proteins become so depleted that generalized edema occurs, intestinal walls become thick, and that if free abdominal fluid is present, stomal narrowing might in all probability take place and retention develop, yet the occurrence of hypoproteinemia in the average patient experiencing postoperative retention would seem to be merely coincidental and not a matter of cause and effect.

SUMMARY

Estimations of the concentration of protein in the serum of patients during the normal postoperative period, after performance of various surgical procedures upon the upper portion of the gastro-intestinal tract, have been carried out.

Such estimations revealed first, a normal decline in the concentration of total proteins as well as a decline in the concentration of the two fractions; this decline was slightly more marked in the case of the albumin fraction than in the case of the globulin fraction. Second, it was found that after the fifth postoperative day a steady and persistent increase occurred in the concentration of both total proteins and the albumin and globulin fractions thereof.

A concentration of total protein of less than 5.2 gm. per 100 cc. frequently was found without gastric retention being present. Concentrations of albumin of less than 3.0 gm. per 100 cc. never were found. Rapid regeneration of globulin was not found.

Estimations of the concentration of serum protein and the two fractions thereof, as well as determinations of colloidal osmotic pressure, were carried out among fifteen patients, after operations on the stomach, in whom the postoperative course was marred by the presence of postoperative gastric retention. Gastric retention occurred in association with a concentration of serum protein that was within normal limits or within normal postoperative limits. Gastric retention was found to occur in association with a colloidal osmotic pressure well in excess of the "critical edema level" (160 to 200 mm. of water).

The fluctuation in the amount of retention was not paralleled in any way by fluctuations in either the concentration of serum proteins or the albumin fraction of the colloidal osmotic pressure. Retention frequently diminished and disappeared with a coincidental decrease in serum osmotic pressure and in the concentration of serum proteins.

The presence of clinical edema, caused by hypoproteinemia, was noticed postoperatively at the same time gastric retention finally disappeared.

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THE IRRITABLE DIGESTIVE TRACT

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There are a number of syndromes which I meet with ever so often and which I feel sure are due mainly to an exaggerated irritability of the digestive tract. Some may be due in part to too sensitive a nervous connection between the brain and the gut, or in the reverse direction, between the gut and the brain. As one can easily see by thinking a moment, not only can the brain disturb the actions of the gut, but abnormal behavior of the gut can easily disturb the brain. This fact soon becomes painfully apparent to anyone who has to suffer from nausea, vomiting, hunger pain, pyloric obstruction, or severe diarrhea.

DISTRESS IMMEDIATELY AFTER EATING OR TAKING AN ENEMA

I always think of hypersensitiveness of the neuromuscular mechanism of the upper part of the digestive tract when a patient tells of pain or distress which comes immediately after food is taken into the stomach. I then ask if the same distress comes immediately after the drinking of water, and particularly of ice water. Usually the answer is, "Yes," and then I am sure the trouble is due, not to the nature of the food eaten, but simply to its mechanical impact on the gastric mucosa, or to the quick stretching of the wall of the stomach and duodenum, with resultant stimulation of the muscle fibers. A toy balloon blown up in the stomach would probably have the same effect.

When I hear this typical story of pain on drinking I know right off that I haven't any chance of ever finding a diet that will relieve the patient's discomfort because surely I will never find anything more innocuous than water. To make even surer that this type of person's indigestion is due purely to an exaggerated reaction of the stomach and bowel to distention, I ask if quick filling of the colon with an enema, even of so bland a fluid as warm physiologic saline solution, will cause cramps and perhaps nausea and belching. Often the answer is, "Yes," and then the mechanism of the pain is the same as in the case of the stomach. The nausea and belching are due probably to reverse ripples running orad from the stimulated segment of gut.

BOWEL MOVEMENTS RIGHT AFTER EACH MEAL

A sure sign of a hypersensitive digestive tract is its tendency to start emptying itself as soon as food is taken; in other words, the person has a call to go to the toilet or a feeling that he may have to go, shortly after each meal. This

is due, apparently, to an exaggeration of that normal tendency for rush waves to start running down the bowel as soon as food enters the stomach or moves into the duodenum. In most persons a bowel movement is likely to be obtained only after breakfast, because then, after the night's rest, the gut is most sensitive and reactive. It is possible that the postcibal tendency to defecation is due also to some sort of reflex between the stomach and the colon.

NERVOUS DIARRHEA

In some few persons with a hypersensitive digestive tract the waves will run on down the bowel so fast after a meal that undigested food will appear in the feces within an hour or two after it is eaten. That the trouble in these cases is a nervous one is indicated by the fact that one rarely finds organic disease to account for it, and the patient usually lives on for years without coming to any bad end. Interestingly, in not a few cases the trouble is hereditary, and on inquiry one can find that several relatives are similarly affected. Characteristic of a nervous diarrhea is its coming in short attacks consisting of only one or two large, soft movements.

THE DUMPING STOMACH

Some sensitive persons suffer immediately after eating from flushing and sweating, with perhaps nausea and weakness, "jitteriness," and faintness. These symptoms make one think of too sensitive a nervous connection between the proximal part of the digestive tract and the brain, and this may be one cause; another is the too rapid outpouring of food into the jejunum, which one can see sometimes while watching with the roentgenoscope. Naturally the symptoms are those which sometimes follow gastro-enterostomy when there is a similar rapid dumping of the gastric contents into the bowel. That this is the cause of the symptoms is shown by the fact that they can be produced by feeding a person too rapidly through a Witzel tube leading into the jejunum.

EXCESSIVE REACTION TO LAXATIVES

One way in which to recognize the patient with a hypersensitive bowel is to ask how he responds to laxatives. Often he will say that the smallest dose of any laxative is likely to produce in him an exaggerated effect.

ALLERGIC HYPERSENSITIVENESS

Highly allergic persons often have a hypersensitive digestive tract which responds violently not only to certain proteins but also to a number of simple chemical substances. Thus, many a hypersensitive allergic woman will say that an aspirin tablet or even ten drops of dilute hydrochloric acid will

promptly tie her intestine into knots! If one were to hear this only once one might be inclined to disbelieve it, but after hearing this type of story from many lips I do not doubt that such sensitiveness exists.

Many of the women with so-called mucous colitis have an overly irritable bowel which, as everyone knows, can react strongly to emotion or to rough or irritating foods or to the taking of some alcoholic drink.

BLOATING AFTER DRINKING WATER

Not a few persons with an irritable bowel complain of a remarkable type of bloating which comes almost immediately after drinking, between meals, a little soda pop, tea, or even water. This bloating appears so suddenly that it would seem that some reflex must be set in motion which causes gas to pour out of the mucosal blood vessels and into the lumen of the gut. Why, in an individual, this phenomenon appears at one time and not at another, it is hard to say. I suspect that the bloating comes when a little solid food is not taken first to keep the liquid from running too rapidly down the bowel, before it has been made isotonic and warmed to body temperature.

SENSITIVENESS OF THE GUT DUE TO A COLD

Sometimes, when a person has a cold, the bowel will become so sensitive that it will cramp or bloat easily, and then, as the patient says, anything he eats will cause discomfort and form gas. In some cases, the patient at this time will suffer for several days with hunger pain which is relieved by eating. The taking of food gives relief probably because it causes a static, painful type of contraction to change into a more comfortable moving contraction or wave which soon pushes accumulations of gas on down the bowel and into the rectum.

DISTRESS AFTER DEFECATION

A peculiar syndrome, due apparently to an exaggeration of normal reflexes arising in the bowel is abdominal distress for a half hour or more after defecation. I have seen it a number of times in highly sensitive Jewish women, and occasionally in men. In its severest forms I have found it in relatives of the insane or the epileptic. For some time after defecation there will be a feeling of weakness or faintness, with abdominal distress or pain, sweating, and mental misery. In none of these cases have I found any disease in the rectum or colon to account for the trouble, and the syndrome appears to be due purely to an exaggeration of that weakness and distress which some people with diarrhea feel right after they have had a large, loose bowel movement. In a few of the worst cases the patient reported having a similar distress after urination or ejaculation of semen.

DISTRESS DUE TO EXAGGERATED REFLEXES FROM THE DIGESTIVE TRACT

Many persons get a headache if they have to go without a meal or wait for their breakfast, and they get relief as soon as they eat, or perhaps drink some coffee. One can imagine that the trouble is due to too sensitive a nervous connection between the gut and the brain. Some persons fill with gas when they get hungry and this is hard to explain; some may have a peptic ulcer. I have seen a few persons who said they resembled arthritics in that their indigestion usually flared up whenever a storm was approaching. I know a woman who may vomit if her skin is suddenly chilled, as when she steps outdoors in winter.

Many persons gag so easily that they cannot brush their back teeth and cannot wear dental plates with any comfort. Some of these persons vomit if they cough or belch for a while. A marked tendency to get car-sick or sea-sick does not seem to be due to any hypersensitiveness of the bowel or of the nervous system as a whole. At sea the dyspeptic may enjoy every meal while the big "husky" with a "cast-iron stomach" is completely knocked out. My impression from some observations is that a tendency to seasickness is inherited.

DIAGNOSIS

Unfortunately, the significance of the syndromes I have described is not always recognized by the average physician, doubtless because so little has been written about them. It is to be hoped that some day they will be better known and understood so that the patients can be spared the expense of repeated medical overhaulings and perhaps one or more futile operations. The diagnosis should be made from the typical history and not from negative reports of roentgenologic studies or of surgical explorations of the abdomen. Fortunately, the symptoms are almost pathognomonic.

ETIOLOGY

As one would expect, an irritable digestive tract is to be found most commonly in nervous, sensitive and overly reactive persons. The physician can usually recognize generalized hypersensitiveness right off from the way in which a patient complains about little things, or the abnormal way in which he or she reacts to some of the discomforts of a medical overhauling. Thus, if a woman "has a fit" over a pelvic or sigmoidoscopic examination, a barium enema, the swallowing of a stomach tube, or the sticking of her ear for a little blood, she must either be hypersensitive or else a "cry baby." Often one can judge of her sensitiveness also by pinching the skin and subcutaneous tissues over the abdomen, or by pressing on the styloid process below the ear. If

with any little ordeal her heart races, or she breaks out in a sweat, or wants to urinate every fifteen minutes, or faints away, one can be sure that her sympathetic nerves are overly excitable or a bit erratic in their behavior.

Especially, when I suspect that a woman's troubles are due to a neurosis, I note the intensity of her knee jerk because if it is so strong as to cause her to jump or quiver all over I will suspect that she is so overly reactive that she must constantly be suffering from the effects of small stimuli too weak to bother most persons.

Some physicians may ask, "Well, if these people are so sensitive all over, how do you know that the digestive tract is particularly sensitive?" My answer is that since I see many generally hypersensitive persons who haven't any of the syndromes described here, I think these troubles must be due to a hypersensitiveness of the *intrinsic* nerves of the stomach and bowel. Long experimentation with rabbits with the vagus or sympathetic nerves cut and the endings allowed to degenerate, convinced me that the surest way to produce a hypersensitive bowel is to destroy the extrinsic nerves and especially the sympathetic group which normally exert a quieting effect on the gut and (in the rabbit at least) keep it from responding to every stimulus. Most of my rabbits, when deprived of this quieting or braking effect, soon died of diarrhea. Just touching the bowel of such an animal would cause it to become active and to start emptying itself caudad.

Probably in most cases, hypersensitiveness of the digestive tract is to be found in a hypersensitive person. Such factors as overwork, illness, strain, unhappiness and insomnia will often have had their influence in making the person nervous, but in most cases the trouble is largely hereditary in nature. In the worst cases I have seen, one or more of the patient's near relatives were insane or epileptic, and I suspected that the hypersensitiveness of the gut was just part of the nervous curse which ran through the family. Perhaps the defect which in a parent was in the brain showed up in the daughter in the autonomic nerves of the abdomen.

In a few cases I have seen the symptoms of a hypersensitive stomach come suddenly with a small stroke which appeared to have left the upper end of the digestive tract as spastic as it did the arm and leg. The fact that poliomyelitis will sometimes cause a striking disturbance in bowel action makes me wonder if in some few cases the irritability of the nerves of the gut may not be a relic of an unrecognized attack of this disease or of some other infection with a neurotropic virus.

PROGNOSIS

The outlook is favorable except in the bad cases of lientery due to an overly irritable bowel. Persons with this disease often suffer for years. Those

with the milder syndromes tend to get better as they grow older and less irritable and sensitive.

TREATMENT

Naturally, in many cases, rest and good nervous hygiene are the most helpful therapeutic measures. Sometimes sedatives will help. I know of no safe way of lowering the over-reactivity and hypersensitiveness of the type of gut which passes food too rapidly from stomach to rectum. Opium may help but it is too dangerous a drug to use for long. When codeine works well it is probably fairly safe. I personally have never seen habituation to codeine and there are only a few cases recorded in the literature. The fact that the bowel probably lacks the normal inhibiting effect which comes from the extrinsic nerves may explain why a nerve-blocking drug like belladonna usually does not help. What is needed probably is more an exciter of autonomic action than a quieter.

Frequent feedings should probably be avoided because each meal starts waves running down the bowel. The patient may do well also to avoid rough foods, which can stimulate the intestinal mucosa. Liquids with meals should be avoided because they will tend to wash food and food residues far down the bowel before their digestion has been completed. Cold foods may be harmful because cold may serve as a stimulus to the gastro-intestinal muscle. Some persons with a hypersensitive bowel are greatly helped by the removal from the diet of one or more foods to which they are sensitive.

Especially with a dumping type of stomach it may be helpful to start a meal with solids rather than with liquids. In bad cases the patient should eat slowly, and preferably while lying down. Persons who bloat suddenly on drinking fluids may avoid trouble by never drinking between meals, or by always taking first some solid food and then sipping the liquid slowly. Sugary fluids should be avoided since in some persons sugar in concentrated form seems to irritate the gastric or intestinal mucosa.

Rest after meals may be helpful because exercise of the abdominal muscles tends to start peristaltic waves. In many cases eating slowly is advisable because this removes that stimulus which comes to the gastric wall when its muscle fibers are quickly stretched.

Patients who have great distress after defecation should be given a low residue diet and taught to empty the bowel only once in several days. In preparation for the ordeal some have learned to take 10 grains (0.65 gm.) of bromural.

Hypersensitive persons who gag easily should keep their teeth as long as possible because, after they lose them, they may never be able to wear plates.

SUMMARY

A number of syndromes are described which are due largely to an overly reactive stomach and bowel, and partly to what, for want of any exact information, may be called too close a nervous hook-up between the brain and the digestive tract. With such hypersensitiveness the brain is often distressed by exaggerated or disordered types of activity in the gut.

Among the symptoms described are distress or pain immediately after distending the walls of the digestive tract by eating food or drinking water, or taking an enema; a feeling that the bowels are going to move after every meal; nervous diarrhea; distresses after eating similar to those seen with a "dumping stomach;" distress after defecation; an excessive reaction to laxatives; bloating after the drinking of water, and bloating or getting a headache when hungry.

Suggestions for treatment are offered.

THE EFFECT OF ANTACID THERAPY ON THE PEPTIC ACTIVITY OF GASTRIC JUICE IN MAN[1]

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INTRODUCTION

Although it has long been recognized that the destructive action of gastric juice is due to the combined effects of free hydrochloric acid and pepsin, various studies (1, 2, 3) on the pathogenesis of gastroduodenal ulcer have emphasized primarily, though not exclusively, the rôle of acid. The significance of pepsin in the development of gastroduodenal ulcer has in recent years received renewed attention. Thus, Schiffrin and A. A. Warren (4) perfused segments of the gastrointestinal tract with acid alone, and with acid and pepsin, and demonstrated that the perfusion of acid and pepsin produced more severe ulceration than the perfusion of acid alone. Schiffrin and Ivy (5) similarly have called attention to the fact that ulceration of the gastrointestinal tract in experimental animals has never been produced by the application of physiological concentrations of hydrochloric acid in the absence of pepsin. Indeed, the histamine-stimulated gastric juice utilized in the production of ulcers by Büchner et al. (6) and by Code, Wangensteen et al. (7) is not only strongly acid but also rich in pepsin, a fact which has been noted by several workers, more recently by Bucher and Ivy (8).

It appeared desirable in view of these observations to determine more directly than had been done hitherto the effect of certain antacids on the peptic activity of the gastric contents in man.

METHOD OF STUDY

A series of experiments was conducted in three adult men, two with duodenal ulcer, and one with no demonstrable organic disease. Two general methods of study were employed.

A. A study of the pepsin inhibiting effect of various antacids (calcium carbonate, aluminum hydroxide, and magnesium trisilicate) administered during the course of a histamine test. These effects were compared with control histamine tests in which no antacids were administered. The histamine test in this study was modified in order to standardize the base line of peptic activity prior to the injection of histamine. Twelve samples of gastric juice were aspirated at 10 minute intervals. Histamine dihydrochloride, in dosage of 0.01 mgm. per kilo. of body weight, was injected subcutaneously following the

[1] This work was supported in part by a grant from John Wyeth & Bro., Inc., Philadelphia, Pennsylvania.

sixth aspiration. The pH value of each sample of gastric juice was obtained with the Beckman glass electrode; determinations of peptic activity were made in duplicate. These procedures were done within two or three hours after aspiration.

To observe the effects of medication, the antacid employed was administered twice during the histamine test—immediately after the histamine injection, and again in the same dosage after the ninth aspiration (30 minutes after the injection). The antacids were administered in the following dosage, usually with very little water.

Calcium carbonate	2 and 4 gms.
Aluminum hydroxide[2]	4, 8 and 30 cc.
Magnesium trisilicate	2 gms.

B. A study was made on one of the patients with duodenal ulcer (M. T.) of the effects of the above mentioned antacids and of hourly milk and cream on the peptic activity of gastric chyme aspirated at regular intervals throughout the day from 8 a.m. to 8 p.m. These values were compared with the pepsin values of gastric juice obtained on a day of fasting with no medication. The program was as follows:

Day 1	Fasting.
Day 2	90 cc. milk and cream mixture hourly.
Day 3	90 cc. milk and cream hourly. 6 small meals.
Day 4	90 cc. milk and cream hourly. Aluminum hydroxide 4 cc. hourly.
Day 5	90 cc. milk and cream hourly. 4 cc. aluminum hydroxide hourly. 6 small meals.
Day 6	90 cc. milk and cream hourly. 2 gms. calcium carbonate hourly.
Day 7	90 cc. milk and cream hourly. 2 gms. calcium carbonate hourly. 6 small meals.

When the time of feedings or medication coincided with the time of gastric aspiration, the gastric sample was removed before the feeding or medication was given. Evening samples of gastric juice were stored overnight since it has been shown that peptic activity remains unimpaired during such a length of time (9).

Method of determining peptic activity. The technique of determining peptic activity employed in these studies was the Beazell (10, 11) modification of the Anson and Mirsky method (12). The procedure was further simplified and adapted for the Evelyn photoelectric colorimeter. *Preparation of reagents.* The phenol reagent was prepared as described by Folin and Ciocalteau (13). The 10 per cent hemoglobin solution was prepared according to methods de-

[2] Amphojel—John Wyeth & Bro., Inc.

scribed by Anson and Mirsky (12) and by Beazell (10). The tyrosine standard was prepared to contain 0.15 mgm. thrice crystallized tyrosine[3] per cc. of solution, and contained 0.5 per cent formaldehyde as a preservative. The other reagents employed were 4 per cent trichloracetic acid, N/8 hydrochloric acid, 3.85 N sodium hydroxide and N/10 hydrochloric acid. The working solution of hemoglobin was freshly prepared for each experiment by diluting 2 parts of the 10 per cent hemoglobin solution with 3 parts of N/8 hydrochloric acid.

Two test tubes containing 5 cc. each of acid hemoglobin solution were placed in a constant temperature water bath at 37.5°C. When the acid hemoglobin in the tubes had reached this temperature (after an interval of about 15 minutes), the contents of one tube were added to 1 cc. of undiluted gastric content, and the contents of the other tube to 1 cc. of inactivated gastric content (inactivated by heating in a boiling water bath for 5 minutes). Thorough mixture was accomplished by whirling the test tube between the palms of the hands and the tubes were then placed in the water bath. Exactly $7\frac{1}{2}$ minutes (by stop watch) after the addition of the hemoglobin solution to the gastric juice, the undigested hemoglobin was precipitated by the addition of 10 cc. of 4 per cent trichloracetic acid to stop further digestion. After thorough mixing the material was then filtered.

One cubic centimeter of the filtrate of the active gastric juice was added to a 100 cc. volumetric flask; to a second 100 cc. flask was added 1 cc. of the filtrate from the inactivated (boiled) gastric juice. 1 cc. of the standard tyrosine solution was also added to the second flask for the purpose of increasing the subsequently developed blue color to a readable intensity. Both flasks were then partially filled with distilled water, and 1 cc. of 3.85 N sodium hydroxide was added to each. After shaking, 1 cc. of phenol reagent was added to each flask. The flasks were then shaken immediately, filled to the 100 cc. mark with distilled water and thoroughly mixed. After an interval of 15 minutes which permitted the blue color to reach its maximum intensity, the color intensity of the two solutions was measured by the Evelyn photoelectric colorimeter using filter No. 635.

The readings so obtained were then converted from a table to mgm. tyrosine per 1 cc. of the filtrate. (The method of establishing the table is discussed below.) The quantity of tyrosine produced by the digestion of the hemoglobin by the 1 cc. gastric juice was calculated from the formula,

$$(x - (y - 0.15)) \times 16$$

in which: x = mgm. tyrosine in the active unknown; y = mgm. tyrosine in the inactivated (boiled) unknown; the figure 0.15 represents 0.15 mgm. ty-

[3] Eastman Kodak.

rosine added to the flask containing the filtrate from the inactivated gastric juice; the figure 16 corrects for the dilution of 1 cc. of gastric juice to 16 cc. This value for tyrosine was then converted into pepsin units per cc. of gastric juice employing the tables of Bucher and Ivy (14).

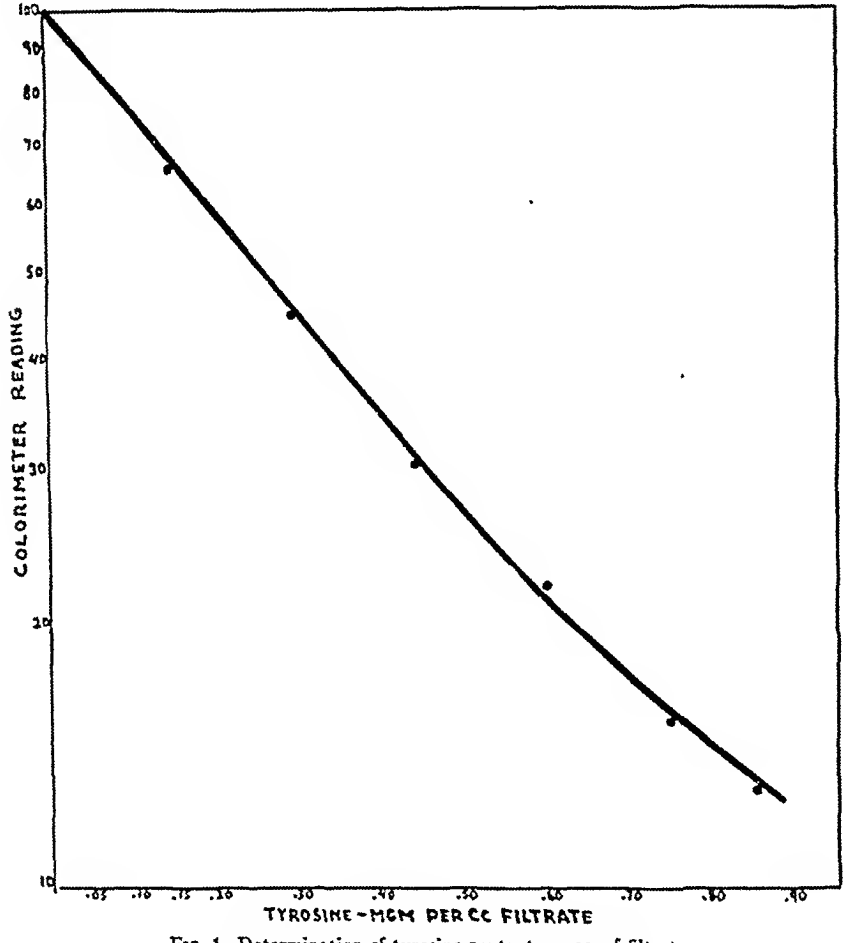

FIG. 1. Determination of tyrosine content per cc. of filtrate

The following method was employed to establish the curve (fig. 1) for tyrosine content in a solution using the Evelyn photoelectric colorimeter. 0.075, 0.30, 0.45, 0.60, 0.75, and 0.85 mgm. tyrosine were added to a series of 100 cc. volumetric flasks, using the appropriate volume of the standard tyrosine solution. 3 cc. of N/10 hydrochloric acid was added to each, and each flask was then partially filled with distilled water. 1 cc. of 3.85 N sodium hydroxide and 1 cc. phenol reagent were added to each and the color developed as in the

TABLE 1

The effect of aluminum hydroxide, calcium carbonate, and magnesium trisilicate on the peptic activity of histamine-stimulated gastric juice in man

		Antacid ↓	Fasting ↓					Histamine plus Antacid ↓		Antacid ↓			
			1	2	3	4	5	6	7	8	9	10	11	12
A.C.	Control		*1399* 1.48	*276* 2.61	*330* 2.00	*330* 1.65	*556* 1.84	*708* 1.81	*1189* 1.41	*1020* 1.29	*917* 1.30	*933* 1.41	*884* 1.32	*967* 1.43
	8 cc. $Al(OH)_3$		*1021* 1.40	*746* 1.73	*686* 1.49	*633* 1.41	*901* 1.42	*1003*	*96* 4.04	*901* 2.11	*985* 1.47	*351* 1.95	*655* 1.81	*729* 1.85
	4 gms. $CaCO_3$		*985* 1.56	*900* 1.62	*726* 1.58	*906* 1.49	*1231* 1.82	*848* 2.36	*548* 6.21	*538* 6.41	*884* 2.11	*340* 6.23	*340* 6.32	*686* 5.98
	2 gms. $CaCO_3$		*361* 3.37	*2.45* 1.74	*362* 1.44	*984* 1.34	*807* 1.29	*1192* 1.31	*517* 5.95	*707* 6.73	*1133* 1.45	*352* 6.66	*505* 6.65	*933* 1.62
	4 cc. $Al(OH)_3$		*641* 2.5	*1115* 1.61	*1133* 1.62	*949* 1.98	*1113* 1.75	*847* 1.77	*580* 5.9	*527* 4.4	*848* 2.3	*276* 3.29	*783* 2.12	*900* 1.70
	2 gms. Mag. Trisil.			*428* 1.69	*569* 1.60	*445* 1.59	*644* 1.69	*627* 1.72	*233* 5.66	*545* 1.89	*321* 1.92	*407* 5.04	*729* 2.11	*828* 1.94
M. T.	Control		*933* 1.71	*985* 1.60	*822* 1.65	*917* 1.58	*839* 1.58	*783* 1.91	*1153* 1.44	*933* 1.36	*884* 1.31	*750* 1.36	*848* 1.33	*933* 1.43
	30 cc. $Al(OH)_3$		*860* 1.35	*820* 1.52	*625* 1.55	*967* 1.52	*967* 1.49	*896* 1.51	*85* 3.9	*835* 1.90	*853* 1.39	*148* 3.38	*782* 2.32	*990* 1.37
	8 cc. $Al(OH)_3$		*750* 1.65	*740* 1.63	*729* 1.65	*666* 1.68	*686* 1.63	*783* 1.54	*191* 3.72	*602* 3.03	*697* 2.42	*117* 3.78	*635* 2.28	*740* 1.72
	4 gms. $CaCO_3$		*613* 1.80	*697* 1.40	*580* 1.85	*613* 1.89	*655* 1.81	*622* 1.86	*180* 6.52	*396* 5.75	*232* 5.68	*0* 6.48	*0* 5.71	*128* 5.53
	2 gms. $CaCO_3$		*848* 2.12	*822* 2.0	*900* 1.91	*964* 1.82	*917* 1.80	*844* 1.88	*418* 5.85	*95* 5.33	*494* 4.59	*117* 5.43	*494* 2.78	*786* 1.48
	4 cc. $Al(OH)_3$		*666* 3.92	*452* 3.19	*822* 2.63	*740* 3.04	*733* 2.28	*793* 2.29	*822* 3.16	*884* 2.01	*708* 2.03	*558* 2.99	*538* 2.91	*602* 2.17
I. S.	Control		*1105* 2.11	*967* 1.92	*822* 1.84	*724* 1.73	*1041* 1.67	*1173* 1.63	*1310* 1.54	*1231* 1.48	*1096* 1.50	*1096* 1.49	*962* 1.62	*950* 1.73
	30 cc. $Al(OH)_3$		*917* 1.82	*934* 1.78	*822* 2.00	*917* 1.87	*985* 1.82	*967* 1.83	*234* 4.2	*761* 2.6	*675* 3.61	*0* 4.35	*21* 4.32	*326* 3.92
	2 gms. $CaCO_3$		*771* 6.32	*810* 3.73	*559* 3.92	*680* 2.88	*245*	*765* 3.05	*297* 6.85	*43* 6.52	*708* 6.09	*581* 6.82	*707* 6.27	*85* 7.58
	2 gms. Mag. Trisil.		*559* 3.72	*633* 3.91	*654* 3.07	*559* 3.31	*916* 1.95	*949* 2.12	*900* 4.51	*1076* 1.75	*1020* 1.52	*298* 6.02	*590* 4.41	*835* 1.96
	8 cc. $Al(OH)_3$		*799* 3.19	*786* 2.45	*797* 1.78	*676* 1.94	*901* 1.99	*967* 1.52	*665* 3.83	*1002* 1.82	*1020* 1.33	*548* 3.63	*949* 1.55	*916* 1.38
	4 cc. $Al(OH)_3$		*729* 3.30	*1003* 1.61	*833* 1.79	*1191* 1.61	*866* 1.85	*1096* 1.41	*675* 3.72	*917* 1.63	*1004* 1.38	*772* 2.52	*1003* 1.53	

The figures in italics are the pepsin values. The figures in regular type are the pH values.

unknowns. A curve was established from the data using semilogarithmic paper and the table was constructed from this curve.

RESULTS AND DISCUSSION

The data are recorded in tables 1 and 2.

These studies indicate that the antacid preparations, calcium carbonate, aluminum hydroxide, and magnesium trisilicate had a definite pepsin inhibiting effect when administered to the human subject. In some cases peptic

TABLE 2

The pepsin content and pH value of gastric juice during ulcer therapy

(One patient)

	Fasting specimen							
	8 A. M.	10 A. M.	12 NOON	2 P. M.	4 P. M.	6 P. M.	8 P. M.	10 P. M.
Fasting	*708* 1.88	*951* 1.21	*985* 1.36	*900* 1.28	*1002* 1.30	*884* 1.61	*933* 1.95	
Milk and cream 90 cc. every hour	*527* 3.48	*635* 2.82	*900* 1.38		*729* 1.60		*772* 1.20	
Milk and cream 90 cc. every hour—6 meals	*949* 1.86		*782* 1.63		*708* 1.90		*835* 1.87	
Milk and cream 90 cc. $CaCO_3$ 2 gms. } every hour	*1020* 1.81	*782* 2.01	*761* 3.98	*483* 4.61	*686* 4.59	*719* 1.81	*718* 2.98	*556* 4.81
Milk and cream 90 cc. $CaCO_3$ 2 gms. } every hour—6 meals	*917* 1.36		*463* 3.72		*665* 4.09		*625* 4.15	
Milk and cream 90 cc. $Al(OH)_3$ 4 cc. } every hour	*772* 1.84	*750* 2.20	*771* 1.89	*807* 1.45	*835* 2.22	*917* 1.50	*933* 1.18	*793* 1.20
Milk and cream 90 cc. $Al(OH)_3$ 4 cc. } every hour—6 meals	*822* 1.74		*614* 2.55		*771* 2.10		*772* 1.78	

The figures in italics are pepsin values.
The figures in regular type are pH values.

activity was markedly reduced. Variations occurred in the magnitude of this effect probably as a result of individual differences in the rate of gastric emptying. 30 cc. aluminum hydroxide and 4.0 gms. calcium carbonate exerted the greatest antipeptic action (figs. 2 and 3). Lesser, though appreciable effects, were noted with 29 gms. calcium carbonate, 8 cc. aluminum hydroxide, 2 gms. magnesium trisilicate (fig. 4) and 4 cc. aluminum hydroxide.

Determinations on gastric content sampled at regular intervals throughout

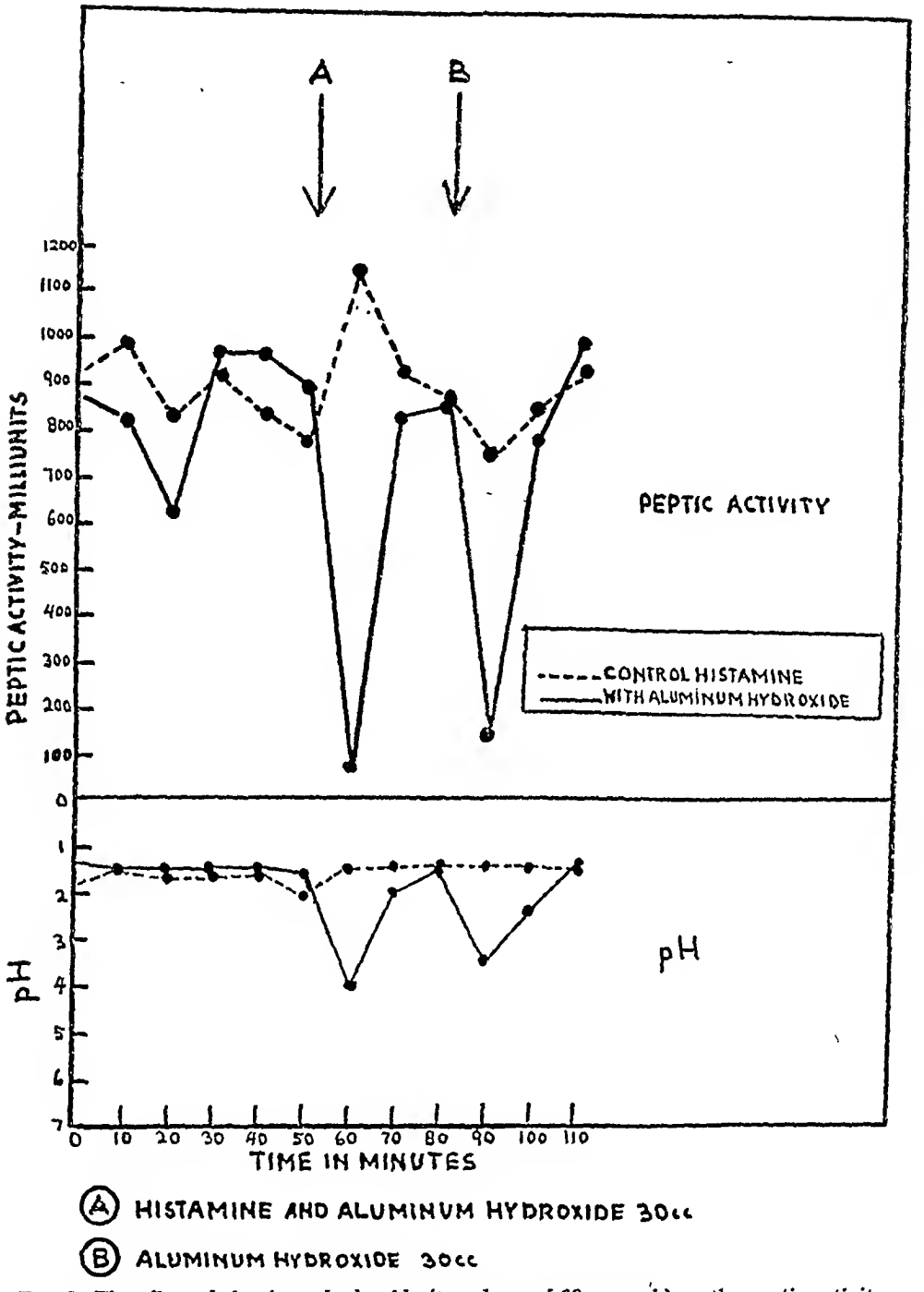

FIG. 2. The effect of aluminum hydroxide (two doses of 30 cc. each) on the peptic activity of histamine-stimulated human gastric juice

the day indicated that the "Sippy treatment" likewise diminished peptic activity (table 2).

In agreement with earlier observations and the more recent ones of Shoch

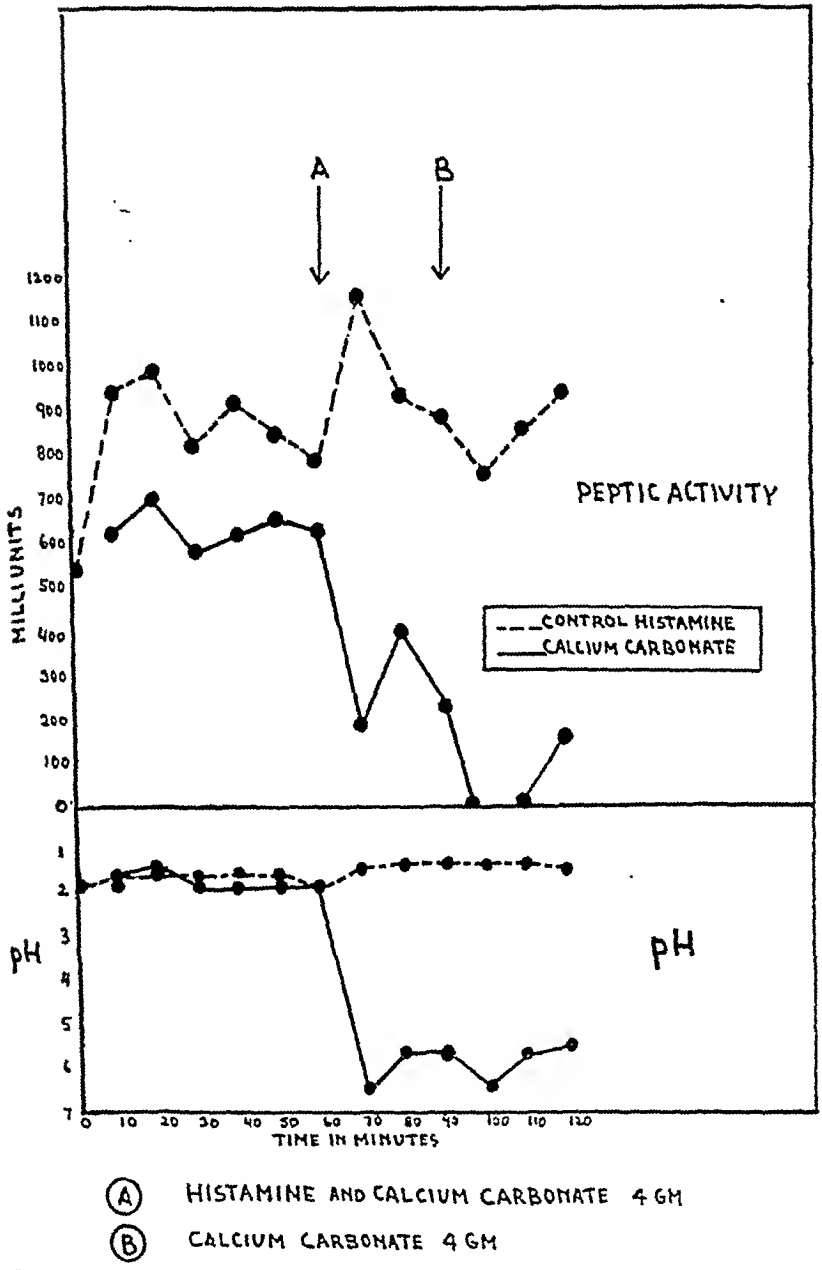

FIG. 3. The effect of calcium carbonate (two doses of 4 gms. each) on the peptic activity of histamine-stimulated human gastric juice

and Fogelson (15) the present studies indicate that pepsin inhibition is brought about chiefly by an alteration in the pH, and that peptic activity decreases

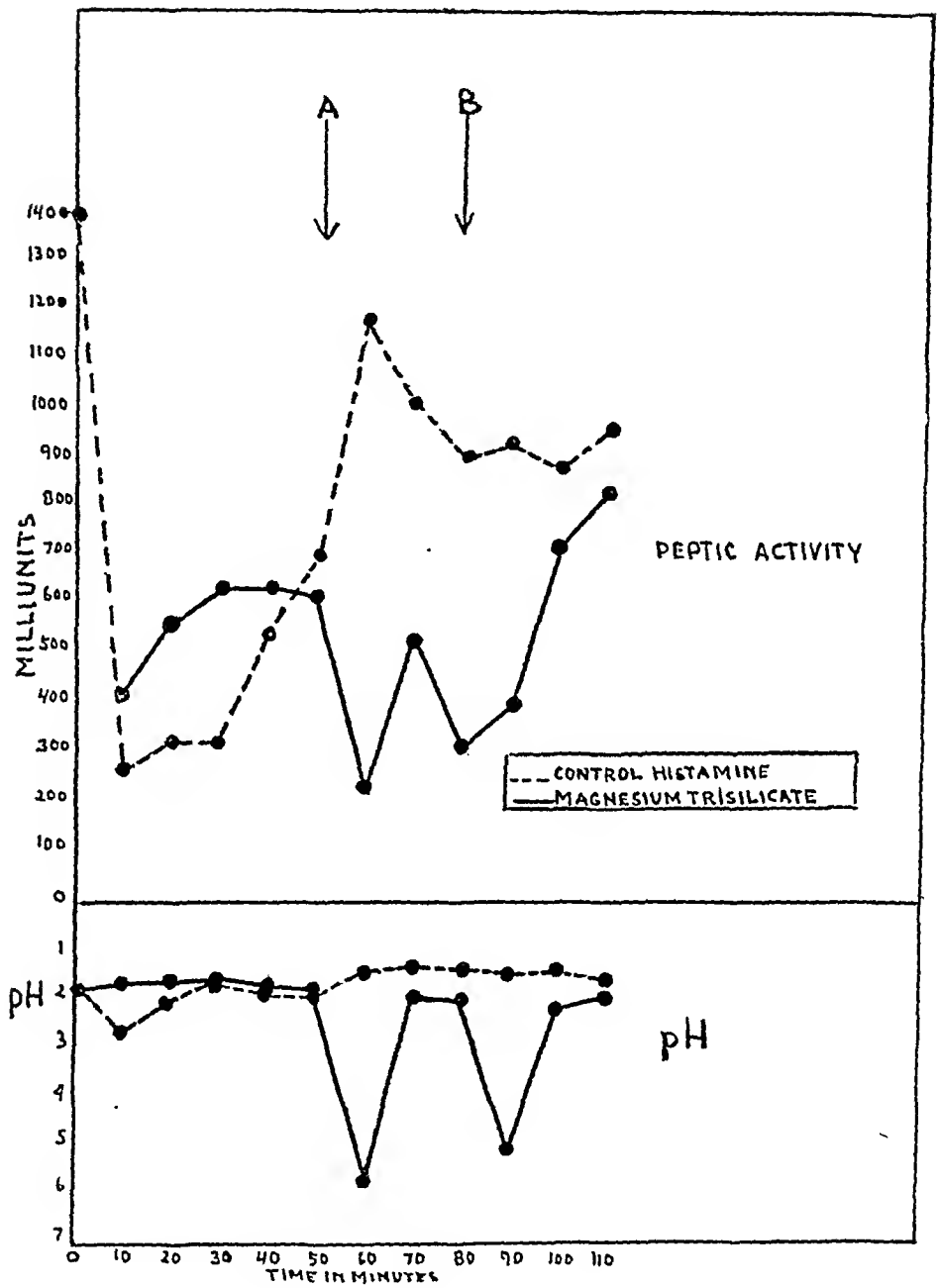

FIG. 4. The effect of magnesium trisilicate (two doses of 2 gms. each) on the peptic activity of histamine-stimulated human gastric juice

as the pH value increases toward neutrality. Aluminum hydroxide appeared to have a greater antipeptic effect than calcium carbonate at the same pH level. For example, in patient A. C., when 8 cc. aluminum hydroxide were

given, the peptic activity at a pH of 4.04 was 96 milliunits. In the same patient the administration of 4 gms. calcium carbonate resulted in a pH of 6.41 and a peptic activity of 538 milliunits. Further demonstration of this point is provided by some in vitro experiments upon a sample of gastric content taken from one patient, as shown in table 3. The various mixtures were stirred at frequent intervals for one hour at room temperature. After centrifuging, 1 cc. aliquots of the supernatant fluid were taken for duplicate determinations. Whenever aluminum hydroxide was added to the gastric juice a precipitate formed. This is in agreement with the work of Komarov and Komarov (16). However, when aluminum hydroxide and strong hydrochloric acid were added to the gastric juice very little precipitate formed, and the peptic activity was high. Schiffrin and Komarov (17) have recently found that

TABLE 3

The in vitro effect of aluminum hydroxide and calcium carbonate on peptic activity of human gastric juice

PREPARATION	pH	PEPTIC ACTIVITY
5 cc. gastric juice 5 cc. water	1.98	1394 milliunits per cc. gastric juice
5 cc. gastric juice 1 cc. aluminum hydroxide 4 cc. water	4.02	86 milliunits per cc. gastric juice
5 cc. gastric juice 1 gm. calcium carbonate 5 cc. water	6.89	360 milliunits per cc. gastric juice
5 cc. gastric juice 1 cc. aluminum hydroxide 4 cc. N hydrochloric acid	1.0	1710 milliunits per cc. gastric juice

both aluminum hydroxide and aluminum phosphate inhibit the peptic activity of canine gastric juice and of commercial preparations of pepsin, not only by the actual precipitation of pepsin under certain conditions but also by two additional mechanisms, namely, (1) at a high hydrogen-ion concentration (pH less than 2) these substances are converted into aluminum chloride, the presence of which inhibits peptic activity, the active principle being the aluminum ion; (2) some soluble compounds of pepsin and aluminum hydroxide or aluminum phosphate are formed which are thought to bring about additional inhibition of peptic activity.

SUMMARY AND CONCLUSIONS

1. Calcium carbonate, aluminum hydroxide and magnesium trisilicate decrease the peptic activity of histamine-stimulated gastric secretion in man.

2. The inhibition of peptic activity, as noted in man, appears to be related to the increase of pH of the gastric juice toward neutrality. However, for a given pH, aluminum hydroxide apparently exerts a greater antipeptic effect than calcium carbonate.

3. The treatment of peptic ulcer with milk and cream mixture, frequent small feedings, and either calcium carbonate or aluminum hydroxide reduces the peptic activity of the gastric contents in man.

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EDITORIALS

THE AMERICAN GASTRO-ENTEROLOGICAL ASSOCIATION STARTS A NEW JOURNAL OF GASTRO-ENTEROLOGY

With this issue, a new Journal of Gastro-enterology makes its bow to the medical public. For some years, the Council and members of the American Gastro-enterological Association have felt a need for a Journal, the editorial and advertising policies of which would be entirely under their control and kept at the highest level of ethics and idealism. Finally, under the able, tireless and courageous leadership of Doctor A. C. Ivy, all difficulties were cleared away: a fine publisher was found who was willing to co-operate 100 per cent, and last June, by vote of the members of the Association, the enterprise was launched.

Success now will depend on the degree of interest shown in the Journal by the members of the Association and all those many physicians who are deeply interested in the advancement of gastro-enterology. Much will depend on the energy and loyalty with which these men tackle the work which, from time to time, will be assigned to them by the editors.

All can now turn to and work with pleasure and enthusiasm for this journal, knowing that whatever they build will be their own, and something in which they can take great pride. As profits come they will be used to help the cause of gastro-enterology and to make an even better and more useful journal.

W. C. ALVAREZ.

BEAUMONT'S EXPERIMENTS ON GASTRIC DIGESTION

The fundamental contributions of William Beaumont to our knowledge of the physiology of the stomach are properly listed among the classics of research. There exists nowhere in scientific history a better example of thorough and competent observation or a more exhaustive use of all the available data, although the latter was secured with the crudest and most primitive equipment. His complete intellectual honesty and his pursuit of knowledge as an end in itself are clearly brought out in the records he wrote; and the great personal sacrifice and inconvenience sustained by him in his efforts to secure the cooperation of the temperamental and erratic Alexis St. Martin are too well-known to warrant repetition.

As a result of the opportunity presented by St. Martin's gastric fistula incurred through a gunshot wound, Beaumont became the first to observe the secretory and motor activity of the stomach *in situ*. He preluded his studies with an exhaustive discussion of the nature of various foodstuffs and their

known behavior in the digestive tract, of the nature of hunger and thirst, and of the motor and secretory activity of the stomach, with a through and careful review of the literature on these subjects. He furnished accurate pictures of the normal appearance of the gastric mucosa, and demonstrated that gastric secretion was elicited only by the presence of food; or to a lesser extent by mechanical irritation. The cephalic phase of secretion was not demonstrated by his experiments, but as a result of his work the axiom of Magendie that gastric secretion is wholly continuous and not phasic was rendered untenable. He had ample opportunity to study the pathological behavior of the stomach after ingestion of irritant material, due to St. Martin's extensive use of liquor.

The presence of free hydrochloric acid in the gastric secretion was established by Beaumont, who proved that it was not sufficient in itself to bring about the far-reaching changes in foods produced by gastric juice. His efforts to determine the composition of gastric secretion led him into collaboration with Dunglison of Virginia and Silliman of Yale, who at that time were recognized as the outstanding physiologist and chemist, respectively, of the country. Through Silliman, a sample was sent to Berzelius, who contributed little beyond the observation that it underwent remarkably little decomposition during a period of five months at Summer temperatures. The active protease, pepsin, was subsequently identified by Schwann.

The manner in which the great majority of the conclusions drawn by Beaumont have been confirmed by subsequent studies attests his attainments as an experimenter and logical reasoner. That some of his conclusions were erroneous is due in part to the primitive nature of his equipment, and in the main to the fact that new interpretations have been placed on his findings, in the light of discoveries made subsequently.

H. GREENGARD.

ULCER PROPHYLAXIS

There can be no doubt that the physical integrity of every able bodied man and woman in this country is needed for a successful outcome of the war, and since it has been the experience of other countries that during the strain of war, peptic ulcer disables an ever increasing number of the civilian population as well as the armed forces, gastro-enterologists are challenged with the problem of preventing, as far as possible, the first occurrence and the recurrence of this disease. Many of us feel that the young man or woman working under strain, who develops hyperchlorhydria, pylorospasm, and the symptoms of heartburn and indigestion resulting from these conditions, can often be detected, and so instructed and controlled that ulcer does not develop; whereas the same individual unguarded and unguided will develop an ulcer. This guidance need not involve so strict a regimen for the individual that his work is cur-

tailed, and indeed most of his pleasureable activities can also be left unrestricted. In fact, the prophylaxis of ulcer initially or in recurrence constitutes the type of life which patriotic men and women really should live at present in order to carry on the burden of the war both in and behind the lines. It is also a comforting thought that the prophylaxis of ulcer, since it involves well chosen food in correct quantities, the best possible use of the time allotted for rest, an appreciation of the importance of both mental and physical relaxation to antidote strain, and adequate exercise, even if it is only the exercise of walking to and from the job, is likewise the best prophylaxis against the other two possible enemies of war workers, cardiac disease and tuberculosis. Ulcer, when prevented by such a regimen, may therefore be said to be a prophylactic disease. The corollary of "Kill two birds with one stone" might be expressed as "Manage your life so as to avoid ulcer and thereby keep your whole body in condition."

SARA M. JORDAN.

INEQUITIES OF THE SELECTIVE SERVICE

To one not officially associated with the workings of the Selective Service Boards and of the Induction Centers, it would appear that much confusion and little consistency surrounds the question of the acceptance or rejection of the individuals who have suffered with peptic ulcer. Uniformity of rulings seem to be lacking. One appeal Selective Service Board accepts any man who has consistently held a gainful job for two years, regardless of medical history. One Center will ignore a past history of peptic ulcer, providing the present radiographic examination is negative. Cases of proven ulcer have been placed in Class 1A, regardless of affidavits of reputable physicians. Other Induction Centers, the wiser ones, reject all cases with histories of ulcer, knowing full well that in accepting such a case they incur the likely risk of early disablement by illness and the likelihood that the soldier will become a lifetime liability on the Federal Government. Already we are being asked to fill out affidavits for one-time inductees who are already being discharged from active service for ulcer-connected disability.

The fault lies probably in the lack of uniform instruction as to procedure rather than as the individual Induction Center or Selective Service Board.

An old ulcer case may remain well for two years, only to have an early recurrence of his illness soon after induction into active service, as all of us have already experienced.

A negative x-ray may obtain in cases of healed gastric ulcer, as is consistent with the accepted facts regarding the life-cycle of ulcer. But, does the negative radiographic report eliminate the possibility of early ulcer recurrence as the result of psychosomatic influences incident to induction into service?

Unfortunately, too, medical affidavits are written with too much complacency by too many physicians, for too many conditions. The results have been to throw a certain and often not unreasonable suspicion of doubt, not so much on the authenticity of such affidavits, but on their true merit and worth. It is probably the experience of every busy phsysician that he could develop a mild case of writer's cramp attempting to comply with all the requests for affidavits, most of which are reasonable, most of which the patient has a legal right to demand and to receive, and in good faith.

Ulcer cases do badly enough in civilian life with its wear and tear. They do much worse under the strain of induction and service in the armed forces of our nation, and of other nations, as noted in the rapidly mounting literature on the increase of digestive disturbances in the populations of Europe, and in the British Armies and Navies and the more recent reports from our base hospitals and naval centers. Like so many other problems in our gigantic and necessarily hurried war effort, the problem of ulcer in the armed forces calls for a uniform control and an unanimity of decision. Lest the country be again burdened after this war, as it was after the last war, with an unnecessarily large number of claims for total disability incurred in the Service; lest an injustice be perpetrated both to the Services and to the individual, let us demand from the responsible heads of the enlistment bureaus and the induction centers of the Navy and the Army, that a uniform policy and a strict surveillance be established to prevent induction of all men who have or who have had a peptic ulcer.

B. B. CROHN.

PREVENTION OF EXPERIMENTAL GASTROJEJUNAL ULCER BY ENTEROGASTRONE THERAPY

Investigations made during the last 10 years have established the existence in the upper intestinal mucosa of a hormone called *enterogastrone*, which depresses gastric secretion and motility. This hormone is chiefly, if not entirely, concerned in the depression of gastric secretion and motility which occurs when fat and sugar in a concentration of 10 per cent or more is ingested with a meal.

The physiological rationale on which the clinical use of cream and olive oil in the diet of the ulcer patient is based, appears to depend on the function of enterogastrone. In view of the role that hydrochloric acid and pepsin play either in the secondary or primary etiology of peptic ulcer, it would appear that enterogastrone has promise of being useful in the management of the disease, especially when hypercontinuous secretion of gastric juice is present.

In the July, 1942, issue of Endocrinology, Hands, Greengard, Fauley, Preston, and Ivy report that the administration of an extract of duodenal mucosa,

rich in enterogastrone potency was remarkably effective in preventing the development of post-operative jejunal ulcer in dogs prepared by the method of Mann and Williamson. This type of animal developes a jejunal ulcer with a lethal outcome in 97 per cent of cases within five months. Eleven dogs were maintained for one year with three injections daily of the hormone and none developed ulcer. Such results might be anticipated, since the corrosive action of gastric juice has been clearly established to be the chief etiological factor in post-operative jejunal ulcer.

A remarkable observation was made after the enterogastrone therapy was discontinued in the eleven animals. All animals failed to develop ulcer during a period of from 8 to 14 months after cessation of therapy. Apparently, the therapy in some manner, "immunized" the animals against the development of ulcer, since most animals develop an ulcer within 10 weeks and all within 6 months after cessation of other types of prophylactic management, such as aluminum phosphate. The nature of the "immunization" was not determined, though gastric analyses were made at frequent intervals. The results revealed that the acidity of the gastric contents had not been permanently reduced by the therapy. However, the gastric secretory studies had not been inclusively designed in advance to elucidate such an unanticipated result of the therapy.

Such experimental observations have obvious implications regarding the management of peptic ulcer in man. Such questions arise as: Can the human patient be "immunized" by a course of injections of enterogastrone? Is human ulcer due to a derangement of the enterogastrone mechanism? The answer to such questions awaits the production of a better product than was utilized in the animal experiments, as well as the chemical isolation and identification of the active principle.

A. C. Ivy.

ABSTRACTS OF CURRENT LITERATURE

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CLINICAL MEDICINE

MOUTH AND ESOPHAGUS

DOCKERTY, M. B. AND MAYO, C. W. Primary tumors of the submaxillary gland with special references to mixed tumors. Surg. Gyn. Obs., 74, 1033 (June 1942).

The changing conceptions regarding the nature of the tumors of the submaxillary gland led to the present review of the clinical and pathologic features of 81 primary submaxillary malignant neoplasms. True mixed tumors constituted 63 percent of this group. These are slowly growing adenocarcinomas; pain and local fixation are usually absent. Adenocarcinomas of the cylindroma type constituted 18.5 percent. These tumors produce pain and local fixation; are of a moderate degree of malignancy but exhibit pronounced infiltrative tendencies with selective invasion of nerves. These tumors tend to recur and present an unfavorable prognosis. There is also found an "intermediate" group of neoplasms which share the pathologic features of cylindromas and mixed tumors. In the series of 81 primary submaxillary malignant tumors, there were 8 patients (9.5 percent) with atypical tumors. The prognosis depended partly on the type and grade of the lesion and partly on the extent of involvement of the regional lymph node.

The authors stressed the disappointing results that follow conservative operations for the extirpation of these malignant neoplasms.

ROBERT TURELL.

SCHATZKI, R. AND HAWES, L. E. The roentgenological appearance of extramucosal tumors of the esophagus. Am. J. Roent. Rad. Therapy, 48, 1 (July 1942).

Six cases of intramural tumors of the esophagus are reported. In three, 2 cysts and 1

neurofibroma, the diagnosis was confirmed. The authors attempt to establish a basic roentgen picture of intra and extra mucosal lesions, and point out that a definite histological diagnosis of intramural lesions is not possible. Of the 6 cases, there were several roentgenologic features in common. In the profile view there is an abrupt sharp angle where the edge of the tumor meet the uninvolved esophageal wall. In the en face view the lesions were sharply outlined in the relief picture. There was no obstruction to the passage of barium. In the large intramural tumors, the esophagus was narrowed in one diameter, while being stretched and widened by the tumor in the opposite diameter, resulting in a slit-like lumen. In the en face view this flattened lumen showed barium irregularly distributed producing a "smear effect." Extramucosal tumors are often demonstrable as large soft tissue masses outside the barium cast. The authors point out that mucosal tumors are less apt to have such a visible soft tissue mass.

MAURICE FELDMAN.

STOMACH

SHAPIRO, N. SCHIFF, L. MAHER, M. M. AND ZINNINGER, M. M. Some observations on atrophic gastritis and gastric cancer. J. Natl. Cancer Inst., 2, 583 (June 1942).

The relationship between cancer of the stomach, atrophic gastritis, achlorhydria and anemia were investigated in 35 patients with gastric carcinoma. Gastroscopic, histologic, clinical and laboratory studies were performed on all of these cases. Large histologic sections of the stomach were employed. Atrophic gastritis was graded into five classes, according to histologic criteria. Results and conclusions: an incidence of 80 percent of atrophic gastritis. Atrophic gastritis occurred more frequently in patients with a long history of digestive disturbances. The incidence of atrophic gastritis and the presence or absence of HCl in the stomach juice were not related to the location of the tumor. Achlorhydria and anemia occurred more often in patients with atrophic gastritis. In the presence of gastric cancer, atrophic gastritis was often overlooked gastroscopically. The frequent combination (80 percent) of atrophic gastritis and gastric cancer in this series suggests a relationship between the two diseases.

H. NECHELES.

JACKSON, C. L., SWALM, W. A. AND MORRISON, L. M. The diagnosis and treatment of chronic gastritis. Rev. Gastro-Enterol., 9, 193 (May, June 1942).

Chronic gastritis has no specific symptom-complex, and requires a careful history, physical examination, gastric analysis, x-ray and gastroscopic study for the diagnosis. The history usually reveals a chain of general and unrelated abdominal symptoms in which pain-distress, periodicity, duration and associated symptoms have no selective definition. The physical findings are even more scarce. Gastric analysis in which careful microscopic slide examination of the gastric and biliary drainage is made has in 67 percent of their cases shown desquamated gastric cells. The x-ray method is of diagnostic value in only about 10 percent, and these are usually of the hypertrophic variety. The only reliable means of diagnosing chronic gastritis is by the semi-flexible gastroscope. Biopsy through an open tube gastroscope from patients in whom the diagnosis of gastritis was previously made with the closed gastroscope confirmed the histologic diagnosis in the majority of instances.

The present methods of treatment of chronic gastritis embrace proper hygiene habits, nervous stabilization, removal of foci of infection, allergic desensitization, dietary regulation, neutralization and absorbent therapy for hyperacidity and HCl in the anacidity problems. Occasionally, gastric lavages in catarrhal gastritis, while more palliative measures include physical therapy and spring-spa waters.

MICHAEL W. SHUTKIN.

(Leading Article.) Dyspepsia in Soldiers. Lancet, 242, 740 (June 20, 1942).

In a Leading Article, the Lancet points out that since the policy was adopted that all soldiers having active peptic ulcer with positive radiological findings should be dis-

charged from the Army, large numbers of men suffering from duodenal ulcer were returned to civil life and as a result new ulcers arising during service seem to be less common. The general view that a soldier with an active peptic ulcer requires invaliding has been widely accepted. There remain many dyspeptics in the Forces in whom no organic lesion can at first be clearly found. They are thought to have gastritis, duodenitis or gastrointestinal neurosis. The frequency of these diagnoses varies considerably in different reports indicating that there is a personal variation (on the part of the physicians) accounting for the wide differences in the figures from different sources.

Referring to gastritis, the Editorial quotes Morton Gill and his colleagues "who throw little light either on causation (which they term obscure), treatment (of which they are frankly pessimistic) or disposal (which they consider a problem likely to remain unsolved)." The Editorial further states that "Too often dyspepsia is regarded as a manifestation of a local organic disease, when in fact it is one expression of a personality disorder or a psychoneurosis". The dyspeptic soldier is often found on questioning to have in addition that group of symptoms usually accepted as due to anxiety neurosis, i.e., exhaustion, dyspnoea, headache, sweating and tightness or pain in the chest on exertion. "His dyspepsia is but the manifestation of a neurosis which in others may be expressed as rheumatism, effort syndrome or frequency of micturition". Treatment and disposal of this large group of dyspeptics,—gastritic, and psychosomatic, or often both combined,—are difficult. Treatment is useless while the man remains in the environment producing his condition. Invaliding is unavoidable. Mental equilibrium is essential.

DAVID J. SANDWEISS.

BOWEL

WILSON, H. Meckel's diverticulum. With a report of twelve cases. Am. J. Surg., 55, 614 (June 1942).

Meckel's diverticulum is a congenital anomaly of the omphalomesenteric duct and was first extensively studied in 1812 by John Frederick Meckel. Diverticulitis and peritonitis were well known but it was since 1925 that ulceration and hemorrhage resulting from heterotopic gastric tissue was adequately studied. It is believed to occur in 2 percent of all individuals and generally manifests itself as a blind pouch extending from the antimesenteric border of the ileum located from 12 to 36 inches proximal to the ileo-cecal valve.

This 12 case series of Meckel's diverticula were operated upon between 1924 and 1941. Males predominated and half occurred in adults. Intestinal obstruction was present in four cases, acute diverticulitis in four, both obstruction and diverticulitis in one; intussusception in one, and in two cases the diverticulum was only subacutely or not at all inflamed. Death occurred in one case complicated by intestinal obstruction. None were preoperatively diagnosed as Meckel's diverticula, though their status as an acute surgical emergency was readily recognized. In none of the 12 specimens was heterotopic tissue found. The entire diverticulum must be thoroughly resected, and finally, a careful search for Meckel's diverticulum must be made in cases where operative findings fail to explain the preoperative symptoms or the peritonitis encountered at laparotomy.

MICHAEL W. SHUTKIN.

HURST, SIR ARTHUR. The pathogenesis of the sprue syndrome. Guy's Hosp. Reports, 91, 1 (1942).

The three features characteristic of and common to sprue, non-tropical sprue and celiac disease are 1) an excess of split fat in the stool without an excess of neutral fat, muscle fibres or starch; 2) demonstration by X-Ray of disappearance of the normal valvular markings of the duodenum and jejunum; 3) absence of specific pathological changes after death. The article contains an outline of the anatomy of the small intestine, and a discussion of the physiology of fat digestion and of the mechanics of fat absorption. Hurst subscribes to the theory that fat is absorbed through the intestinal villi by a pumping action after the fat has been split to fatty acids and glycerin and the fatty acids are made absorbable by the ac-

tion of the bile acids. It is the presence in the stool of large amounts of fatty acid crystals that serves to differentiate the sprue syndrome from the syndrome of pancreatic insufficiency, in which the fat excess is present as neutral fat. He also believes that the term "sprue syndrome" should be applied to the picture presented by such diseases as tropical and non-tropical sprue, celiac disease and idiopathic steatorrhoea. The above mentioned features are the characteristic ones. Additional symptoms, such as hypocalcemia, tetany and bone changes, anemia, glossitis, achlorhydria and vitamin deficiency may also occur but are not uniform in their appearance.

Hurst suggests that these characteristic features of the sprue syndrome results in most instances from a paralysis of the muscularis mucosae. This leads to a loss of the pumping action of the villi and failure of fat absorption. Flattening of the valvulae conniventes also results. The paralysis of the muscularis mucosae is explained as being due to loss of function of Meissner's plexus, which may result in turn to vitamin deficiency or to the action of some toxin on the plexus. The sprue syndrome may likewise result from diffuse mesenteric disease, in which case hindrance of fat absorption takes place at the mesenteric glands rather than at the villi.

HENRY TUMEN.

HUSCHKA, M. The child's response to coercive bowel training. Psycho-somatic Med., IV, 301 (July 1942).

Psychiatrists treating children are confronted frequently with clinical material in which the frame-work of neurosis stands out clearly. Thus, the psychopathology of childhood offers an important field for research and systematic study by analysts in this area should contribute eventually to a better understanding of the neuroses. Data are presented from the analysis of a 3½ year old child whose presenting symptom was obstinate constipation and from a study of the management of bowel training in a group of 213 so-called problem children. "Bowel training" is used in this investigation to mean training the child to forego his infantile custom of defecating when and where he pleases and to substitute elimination at a given time and in a given place. "Coercive training" denotes premature institution of a toilet training regime and overactive, destructive training methods.

The 3½ year old boy had been extremely constipated for one year, ever since the nurse who had taken care of him since birth, had left the employment of his parents. Excellent pediatric care had been unable to effect a cure. The anamnesis and analysis revealed coercive bowel training to have been the cause for the constipation, from which state the young patient was cured due to the analysis. Study of the group of problem children revealed also that prematurely early and coercive bowel training habits, undoubtedly, contributed materially to their psycopathological patterns. There is no basis in the findings of the study for saying that these children like the boy analyzed have developed neurosis, but it is significant that their immediate response to exacting bowel training was in terms of the stuff by which neurosis often manifests itself: constipation, loose stools, anxiety, rage, negativism, excessive cleanliness, guilt".

FRANK NEUWELT.

MILLER, G. Carcinoma of the colon and rectum. Can. Med. Ass. J., 46, 565 (June 1942).

Two important considerations in connection with carcinoma of the colon and rectum are: early diagnosis and adequate removal of the growth with low mortality. Early diagnosis depends upon the education of the lay public as much as of the medical men. One writer reports that his increase of operability of patients from 54 percent to 86 percent was due to operating in the presence of metastases as well as carrying on the educational program. The author adds a third factor—economic considerations keeping patients away from the doctor because the symptoms are not sufficiently severe to cause him to seek relief.

The author discusses the symptoms that are to be expected in the early stages of carcinoma. Patients over 40 years of age, with any symptoms whatsoever referable to the lower left quadrant such as slight

cramps, constipation, gas, dark blood should be regarded as having carcinoma until proved otherwise. Diagnostic methods are discussed. The author stresses the advisability of routine protoscopic examinations since 70 percent of the growths are within the reach of this instrument. Dependence must be placed upon the x-ray for picking up the remaining 30 percent. In secondary anemia of unknown origin, carcinoma of the caecum must be ruled out. Published mortality statistics of cases where carcinoma of the rectum or colon has been removed range from 3 to over 50 percent. Infection seems to be the greatest single cause of these deaths. This can be circumvented by chemo-therapy, a Devine de-functioning colostomy and a simple method of aseptic anastomosis which the author describes. Pre-operative care such as transfusions, high vitamin diet and adequate fluids should be observed.

IRA MANVILLE.

FALK, V. S. Familial polyposis of the colon. Arch Surg., 45, 123 (July 1942).

Polyposis of the colon is a condition in which adenomatous tumor grows from the wall of the bowel and projects into the lumen. Polyposis is divided into two types: 1. the adult or acquired type, which usually follows a chronic inflammatory process; 2. the familial type, which involves the entire colon and rectum of young adults and shows a definite hereditary tendency. We are interested in this second type.

This is a study of a family of 7 children in which 6 showed multiple polyps of the colon. Three of them males and three females. Two of these children, both males, died after carcinomatous degeneration. The father of these children died at the age of 48 of carcinoma of the rectum after a 25 year history suggestive of multiple polyposis. The paternal grandfather died at the age of 30 of "cholera morbus". In one of these cases, permanent ileostomy was done, and patient will probably submit to total colectomy and posterior resection.

Symptoms and signs commonly found include diarrhea, intermittent blood in the stools, abdominal cramping, loss of weight and anemia. Polyps may be palpable in the rectum, but roentgen examination of colon establishes diagnosis and reveals extent of disease. Early and radical operation is treatment of choice.

FRANCIS D. MURPHY.

SUSSMAN, M. L. AND WACHTEL, E. Granulomatous jejuno-ileitis. Radiology, 39, 48 (July 1942).

The authors describe 23 cases of Granulomatous Jejuno-Ileitis. The most striking symptoms were diarrhea and abdominal pains. The stools were usually watery, loose or nonspecific in character. The average loss of weight was fourteen pounds and the temperature was elevated. Signs of obstruction were present in only four cases. In 25 percent of the patients, no free HCl acid was found. The same percent showed perianal abscesses. Clubbing of the finger was found in 40 percent of the series. The authors discuss the pathological findings as they had the opportunity to examine the specimens of the affected areas. They are able to distinguish between the acute, sub-acute and chronic stage. The roentgen findings closely follow those observed pathologically. In the acute phase, differentiation from the non-specific abnormalities described in avitaminosis, sprue, etc., cannot be made. There is patchy segmental distribution of the barium throughout the small bowel. The valvulae conniventes appear farther apart. The outline of the barium-filled jejunal loops is hazy.

In the subacute phase, the jejunal loops show more pronounced alterations in contour. The barium is not distributed evenly and there appears to be irritability, since the barium passed rapidly from loop to loop so that it is difficult to obtain a mucosal pattern. In the ileum the loops appear thickened and more rigid. There is a marked discontinuity in the barium as it is deposited on the mucosa, so that the pattern is fragmented. There is no definite stenosis. In the chronic phase the two characteristics of the chronic phase are pipe-stem loops and multiple stricutes. The terminal ileum is not regularly involved. There was no constant change in the motility of the small bowel, as the disease progressed from phase to phase under observation, nor was

there any significant change in motility or small bowel pattern during intensive treatment with liver and vitamin B. Atropine administered until dryness of the mouth was obtained did not change the configuration of the small bowel.

FRANZ J. LUST.

PENDERGRASS, E. P. AND CHAMBERLIN, G. W. The roentgen diagnosis of lesions involving the ileum, cecum and proximal ascending colon. Am. J. Roent. Rad. Therapy, 48, 16 (July 1942).

A general description of the roentgen diagnosis of lesions involving the right bowel is presented by the authors. The common conditions affecting this portion of the bowel, with the differential roentgen diagnosis are discussed. It is emphasized that in the presence of a colon lesion, reflex spastic obstruction of the terminal ileum may occur. Most early lesions of the ileum and cecum are evidenced by rapid motility. In ulcerative colitis, the roentgen appearance depends upon the stage of the disease. The proximal bowel is not usually involved, until very late. The hyperplastic mucosal patterns with polypoid appearance can be disclosed by the contrast enema. In amebic colitis, the earliest evidence is irritability and spasm of the cecum. The ileum is not generally involved. The cecum is cone or pouch shaped. The exact diagnosis of amebic colitis cannot be made solely by roentgen methods.

MAURICE FELDMAN.

INGELFINGER, F. J. Intermittent volvulus of the mobile cecum. Arch. Surg., 45, 156 (July 1942).

This report demonstrates that by means of recently developed technics in the field of gastrointestinal investigation, the diagnosis of mobile cecum with intermittent volvulus can at times be established during the chronic preobstructive phase of the disease. Strictly speaking, the mobile cecum is no abnormality at all, and has been shown that the cecum in all but 6 percent of persons is completely invested by peritoneum and carries no mesentery. If the term mobile cecum is to have any clinical significance, its applications should be limited to a cecocolon which usually lies in its proper position but which potentially is subject to a process of rotation in the intact abdomen of the living person.

Single white woman of 20 entered the hospital, complaining of intermittent attacks of pain in the lower part of the abdomen which began six years before and had gradually increased in severity, frequency, and duration. Immediately preceding admission, she had suffered two attacks which were complicated by nausea and vomiting. She complained of mild "indigestion" and severe constipation. An appendectomy had been performed previously with no improvement. Roentgenograms taken of this patient demonstrate that in the intact abdomen: (1) the ceco-colon could easily rotate through an angle of 180 degrees and stimulus for this rotation need be no more than single bodily movement, (2) transient intestinal obstruction due to cecal volvulus could occur. By using two modifications of the Miller-Abbott method of small intestinal intubation, the possibilities of diagnosing mobile cecocolon are increased.

FRANCIS D. MURPHY.

WEBER, H. M., KIRKLIN, B. R. AND PUGH, D. G. Lymphoblastoma primary in the gastrointestinal tract. Am. J. Roent. Rad. Therapy, 48, 27 (July 1942).

The authors use the term lymphoblastoma in a broad sense to denote the pathologic process. 34 cases of lymphoblastoma of the gastro-intestinal tract are recorded. Of these, 25 were situated in the stomach, 3 in the small intestine and 6 in the large intestine. In the stomach the diagnosis was not made in any instance, was usually that of carcinoma. In the large intestine 6 cases, 2 were manifested as an intussusception, in one there was a large sessile polypoid lesion. In three cases there was an encircling deformity.

Lymphoblastomas of the gastrointestinal tract are roentgenologically manifested in various ways, but no characteristic picture of the histological nature of the lesion can be determined. A number of differentiating signs are discussed, but the authors offer no suggestions as to how to distinguish them

roentgenologically from other types of neoplastic lesions.

MAURICE FELDMAN.

LUKINS, J. B. Appendicitis in Kentucky. Southern Med. J., 35, 638 (July 1942).

Lukins reports the results of a survey of all the cases of appendicitis in 26 hospitals in the state of Kentucky for the year 1940. 95 deaths occurred in a series of 4,081 patients, a mortality rate of 2.3 percent. Practically all the fatal cases consisted of those patients operated upon more than 48 hours after the onset of symptoms. According to the author, there is practically no mortality if operation is performed within the first twelve hours; it increases rapidly after a delay of forty-eight hours. The appendix had ruptured in 476 cases. It was striking to note that 474 of these patients had received purgatives. Further emphasis is given to the wisdom of early operation in cases of ruptured appendicitis. The author also advocates in such cases the use of blood transfusions, sulfanilamide powder intra-abdominally, avoidance of gauze drains, and incomplete closure of the wound. The chief causes of death revealed by this survey were (1) delay in making the correct diagnosis and (2) the use of purgatives. Lukins properly concludes that if greater concentration were applied to these two factors, the mortality rate in appendicitis would be materially improved.

JOSEPH B. KIRSNER.

ENEBOE, P. L. Spastic constipation. Rev. Gastro-Enterol., 9, 198 (May, June 1942).

This report is based on a review of one hundred seventy-five adult patients whose principal complaint was constipation. All received complete clinical and laboratory examinations, but only one hundred forty-nine had typical spastic constipation. The management recommended involves control of nervous instability, combined rest, regulation of bowel habits, adequate fluid intake, non-irritating diet and occasionally the use of mineral oil or agar agar preparations. Antispasmodics and sedatives are frequently necessary. In this group there were one hundred twenty patients with satisfactory response to this regime.

MICHAEL W. SHUTKIN.

LIVER AND GALL BLADDER

BLACKFORD, S. D., BIRD, R. M., JR. AND CASSCELLS, S. W. Non-operative results in ninety patients with abnormal cholecystograms. Ann. Int. Med., 16, 1118 (June 1942).

Of a group of 500 abnormal cholecystograms but not operated on, 90 were selected as satisfactory from the standpoint of replies. The average period of follow-up was six and one-half years; females predominated in a ratio of 5 to 2; 25 had no gall bladder symptoms, 26 had moderate symptoms and 37 had severe symptoms. 69 had no demonstrable stones. 29 had non functioning gall bladders and 40 had poor function; 33 had symptoms too mild to justify operation, trial therapy was decided in 9, operation was recommended but refused in 23 and surgery was thought too great a risk in 17. The exact medical treatment was known in 57. It consisted of a bland diet, adjustment of the fat content to the patient's tolerance, antispasmodic drugs, choleretic drugs occasionally and sedatives as necessary. Ten of the 90 came to operation. From the standpoint of results, 15 were reported dead; in 11 of these death was attributed to causes outside of the biliary tract; satisfactory results were reported from 47 percent in those recorded as having abnormal cholecystograms; 52 percent in those with poor function, 44 percent in those with no function and 42 percent in those with stones.

Recognizing the fallacies in questionnaire follow-ups, it seemed apparent that no appreciable difference in results were noted in those who followed the program outlined and in those who did not. A group from the same institution measured by the same standards and subjected to surgery showed satisfactory results in 79 percent of the cases with stones as compared with 43 percent treated without surgery. However, the 3,6 operative mortality was about the same as that from biliary causes in the non-surgical group.

VIRGIL E. SIMPSON.

GOETTSCH, E., LYTTLE, J. D., GRIM, W. M. AND DUNBAR, P. Amino acid studies. I. Plasma amino acid retention in the hypoproteinemic dog as evidence of im-

paired liver function. J. Biol. Chem., 144, 121 (June 1942).

Attempts have been made to evaluate liver function by determining plasma amino acid N after intravenous injections of single amino-acids into animals whose livers have been injured by various chemicals. Extirpation must involve 80 to 90 percent of the liver before there is any reduction in deamination and urea synthesis. In humans with liver disease, it was felt that little or no information could be gained by injecting amino-acids unless very severe liver destruction was present. Animals placed on a very low protein diet and experiencing hypoproteinemia as a result seemed to show impairment in liver function that paralleled the decline in serum albumin. The authors report on blood amino-acid N time-curves in normal and in hypoproteinemic dogs. Casein hydrolysate was used as a source of amino acids. In order to determine the speed of metabolism of the casein hydrolysate, appropriate tests were made on the urine. In all the dogs, as hypoproteinemia developed the curves showed progressive retention of plasma amino acids. Following the intravenous injection of casein hydrolysate in a normal animal, the plasma amino acids reached a peak in 5 minutes and returned to pre-injection levels in 20 minutes. In hypoproteinemic animals following intravenous injection, plasma amino acids rose higher and were cleared from the blood stream less rapidly, so that the pre-injection level was not reached until 1 hour later. This retention occurred 1 week after the low protein diet was begun. At later intervals, the retention was even more marked. One dog failed to eat and his curve at this time showed no retention. It is not clear how a failure to accept carbohydrate and fat could produce a favorable change. After 20 weeks plasma amino acid retention was maximal.

In normal dogs, practically all the injected amino acids disappeared from the blood stream within the first 15 minutes after injection. This is due to absorption by the tissues. Calculations are presented to show that the retention is actual and not spurious or relative. During fasting the plasma amino acid level remained constznt although muscle wasting and hypoproteinemia developed. There was no correlation between plasma amino acid values during asting and the fall in plasma albumin. The metabolism of casein hydrolysate given intravenously or by gavage remains essentially unchanged throughout the course of progressive hypoproteinemia. An increase in ammonia and urea excretion occurs. Most of the ammonia is excreted immediately but there is a short lag in urea excretion. Casein hydrolysate injected intravenously failed to stimulate urea clearance. Amino acid clearance was minimal.

IRA A. MANVILLE.

FOSS, H. L. Recurrent biliary tract disease subsequent to previous cholecystic operations. Penn. Med. J., 45, 934 (June 1942).

Foss presented personal statistics of 2500 operative cases for cholecystic disease. Of their number 5.6 percent represented secondary operations on the biliary tract. He indicated that the incidence of secondary operations was large because of incomplete procedures at the time of the first operation; that trauma to the common duct was an important factor in recurrence of symptoms; and that no gallbladder should be removed, or even drained, unless it is clearly diseased—then it should be removed.

H. J. SIMS.

SNYDER, C. D. Some vascular responses within the liver and their interpretation. Rev. Gastro-Enterol., 9, 230 (May, June 1942).

This experimental study is concerned with the responses of the intrinsic vasculature, flow-rates and volume changes of the turtle's liver as evoked by adding cholinergic and adrenergic agents to the perfusing fluid. Acetyl choline was used for the first type and adrenalin for the second. The hepatic artery and all inflow, excepting the portal vein, were tied off; the hepatic vein and portal vein were then cannulated. The cholinergic effect revealed differences in flow rates indicating a decrease in liver volume. The adrenergic effect also point toward a decrease in liver volume. The hypothetical analysis of this data suggests that the acetyl choline constricts the hepa-

tic venous vessels and that the adrenergic agent has no effect, or if any, only a much delayed relaxing effect on the hepatic venous vessels.

MICHAEL W. SHUTKIN.

DELOR, C. J., MEANS, J. W., SHINOWARA, G. Y. AND BOOTH, E. J. A critical study of the diagnostic procedure in gallbladder disease. Rev. Gastro-Enterol., 9, 239 (May, June 1942).

The purpose of the report was to analyze the cholecystographic and biliary drainage findings in 383 patients, of which 102 were subjected to surgery. A comparison between oral and intravenous cholecystography was made in addition to correlating the findings from biliary intubation.

The results of cholecystography indicate that the reinforced oral and the intravenous techniques are superior to the single oral dye method. The reinforced had a higher incidence of visualization than any other, and they have never been successful in the visualization of a gall bladder by the intravenous method when the reinforced technique had failed. The results following biliary drainage inferred that the ability of the gall bladder to concentrate "B" bile is not in direct ratio to it's ability to concentrate sufficient dye to visualize on a cholecystogram. The microscopic findings of cholesterol crystals and calcium bilirubinate pigment in specimens of "B" bile indicate disturbed bile chemistry, but are not pathognomonic for stone. The bacteriologic culture of bile is a valuable procedure especially if autogenous vaccine therapy is contemplated. Although hepatic disease frequently accompanies gall bladder disease, yet as far as cholecystography is concerned, cytological damage of the liver parenchyma does not necessarily affect visualization of the gall bladder unless the histopathology is moderately severe.

MICHAEL W. SHUTKIN.

PANCREAS

BOWERS, R. F., LORD, JR. J. W. AND MC SWAIN, B. Cystadenoma of the pancreas: report of five cases. Arch. Surg., 45, 11 (July 1942).

This is a presentation of five cases of cystadenoma of the pancreas. It was found that in four out of five cases, there was a definite history of antecedent biliary tract disease. Four cases had abdominal masses, the other one had none. Two of the patients had mild diabetes, one had moderate diabetes, other two none. In two cases there was increased severity of diabetes shortly after operation, but manifestations readily controlled.

In X-ray examinations, a soft tissue mass could be seen in the upper left quadrant of the abdomen in 4 of the 5 cases. Gastrointestinal series were made, in 4 there was definite displacement of the stomach. Enemas of varium sulfate were given in 4 of the 5 cases; in all 4 the transverse colon was displace caudad. An operative finding of great importance was the presence of a dilated splenic vein intimately associated with the cystadenoma of the pancreas in 3 of the 5 cases. During the course of removal of a cyst, in one case, the splenic vein was injured and bled profusely. The gross and the microscopic pathologic appearance of these specimens were constant. Cysts smooth, well encapsulated, multilocular and filled with clear or turbid fluid. The cyst lining was of high columnar or cuboid epithelium with clear cytoplasm and basal muclei.

FRANCIS O. MURPHY.

ULCER

SCHENKEN, J. R., BURNS, E. L. AND MASS, U. The role of hypertension and pancreatic erosion in massive fatal hemorrhage from gastric and duodenal ulcers. Surg. Gyn. Obs., 74, 1058 (June 1942).

From 1935 to 1941, the bodies of 81 patients who died at the Charity Hospital of Louisiana as the result of gastric or duodenal ulceration were subjected to postmortem examination. Nineteen (23.3 percent) of these patients had died of hemorrhage; eleven of these had had hypertension. Four of the 19 patients had erosion of the pancreas without hypertension, and 3 had both pancreatic erosion and hypertension.

ROBERT TURELL.

HANDS, A. P., GREENGARD, H., PRESTON, F. W., FAULEY, G. B. AND IVY, A. C. Prevention of experimental gastrojejunal ulcer by enterogastrone therapy. Endocrinology, 30, 905 (June 1942).

The authors have previously reported that enterogastrone (an extract prepared from the upper intestinal mucosa) depresses the motor and secretory activity of the stomach. In an effort to determine its effect on Mann-Williamson ulcers, they treated a series of 25 Mann-Williamson dogs. The animals were injected intravenously at about 10 A.M., 4 P.M. and 10:30 P.M. with 50 mgms of the preparation dissolved in a small quantity of water every day except Sunday, when the animals received only two injections. A series of 10 Mann-Williamson dogs were used as controls and were treated with an extract of pork muscle prepared according to the method for making the enterogastrone preparation. The muscle extract was administered in the same amount and at the same frequency as the enterogastrone preparation. This type of muscle extract was considered essential in the experiment in order to determine whether the enterogastrone preparation has a specificity in action.

All of the 10 Mann-Williamson dogs treated with the pork muscle extract died of jejunal ulcer in from 4 to 30 weeks, the average postoperative survival time being 15.7 weeks. The muscle extract did not inhibit gastric secretion or motility. Of the 25 Mann-Williamson dogs injected intravenously with the enterogastrone preparation, only 6 dogs (24 percent) developed jejunal ulcers. Eight of the 25 animals died within 9 months without ulcer, living on the average 19 weeks following the operation without developing ulcer. Eleven dogs are still alive without ulcer for more than 9 months and 7 of these 11 animals more than one year. Five of the latter 7 dogs have been without treatment for from 4 to 5 months without developing ulcer. Gastric secretion studies were not done on these animals.

The authors are of the opinion that the enterogastrone extract employed by them, even tho as yet impure, and even tho known to produce refractoriness in about 25 percent of the dogs, has a remarkable potency in preventing jejunal ulcer in Mann-Williamson dogs. They are of the opinion that the extract on repeated administration, produces long-standing "immunity" against the development of Mann-Williamson ulcers.

DAVID J. SANDWEISS.

TUTA, J. A. AND BATKO, J. B. An acute perforated duodenal ulcer following metrazol therapy. Am. J. Med. Sciences, 204, 107 (July 1942).

The authors cite the case of a woman, aged 52, who entered the hospital 5 days after receiving an injection of Metrazol for involutional melancholia. One or two injections had been given previously. She died 6½ hours after admission and at autopsy there was found a punch-out perforation of the duodenum in the anterior of the first portion of the duodenum, 1 cm. from the pylorus. By microscopic examination the anatomic diagnosis was generalized fibrinopurulent peritonitis, acute perforated duodenal ulcer and fatty degeneration of the liver. An attempt to explain the way in which metrazol could produce peptic ulceration necessitates consideration of vascular and neurogenic factors. Certain neurogenic impulses can have profound effects on the terminal vascular system of the gastro-intestinal tract. (Boles and Riggs). Stimulation of the vegetative centers may cause peripheral stasis or vasoconstriction through an imbalance of the sympathetic and parasympathetic nervous systems. This concept is essentially that used by Cushing to explain the pathogenesis of peptic ulcer. In summary the authors state that in view of the rarity of this type of complication following metrazol injections, the possibility of coincidence must be considered.

ALLEN A. JONES.

RUBIN, S. AND BOWMAN, K. M. Electroencephalographic and personality correlates in peptic ulcer. Psycho-somatic Med., IV, 309 (July 1942).

Previous studies have demonstrated a rather consistent relationship between one of the characteristics of the electroencephalogram and the fundamental personality structure of the individual. It was found that a high

alpha index characteristically is associated with a passive, dependent, receptive attitude towards other persons when this attitude is freely accepted and not thwarted or inhibited internally; low alpha indices are associated usually with a consistent, well-directed, freely indulged drive to activity. Appreciation of two factors—1., the claim that peptic ulcer cases are associated with a definite personality constellation, and 2., the EEG may be influenced by personality factors—suggest a very sound rationale for the present investigation. An unselected series of 100 male ulcer patients were studied, both from the point of view of the EEG and the personality data. The results are extremely interesting. 71 percent of the peptic ulcer cases showed a dominant or high alpha index in contrast to but 20 percent for a normal group. 20 percent of the ulcer cases had a low alpha index, which is about the normal percentage. As can be seen from these figures very few ulcer cases constituted the middle groups, which include the majority of normal individuals as determined by the alpha index. Personality studies of these 100 ulcer cases correlated very nicely with the EEG findings as to alpha indices—most of them showing passive dependent attitudes (high alpha index), and the rest show a "reaction formation" to this underlying passivity (rare or low alpha index).

FRANK NEUWELT.

SURGERY

WILENSKY, A. O. Retention of the sphincter in the radical operation for carcinoma of the rectum and rectosigmoid. New York State J. Med., 42, 1150 (June 1942).

There are two types of carcinoma in this region. Squamous celled carcinoma arises from the anal canal. It spreads caudad towards the perineum. In this type radical operation demands removal of the sphincter. Adenocarcinoma is the more frequent tumor, and has its origin in the rectal mucosa. The direction of spread is upwards to the mesorectal lymph nodes. In such cases retention of the sphincter is permissible. A radical operation with conservation of the sphincter is possible when the lower border of the tumor is at least 3 inches from the anal margin, and if there is a long mobile sigmoid and meso-sigmoid. The usual criteria for radical operability apply, such as, not too many adhesions to neighboring viscera, absence of extention of the tumor into the pelvic wall, limitation of lymph node metastasis, and the absence of distant abdominal metastases. A relatively good blood supply can frequently be obtained. If much marginal necrosis takes place, a fecal fistula may form. Different operative procedures and surgical technics are discussed, and eight cases are summarized.

PHILIP LEVITSKY.

MACDONALD, D. The preoperative care of the patient with gallbladder disease. Penn. Med. J., 45, 927 (June 1942).

Macdonald stressed the essential requirements for the preoperative care of patients with gallbladder disease. These requirements were divided into general and special care. The general care included the correction of anemia, the removal of infection, the production of a normal water balance, the correction of poor circulation, a preoperative hospital stay, the correction of weight, and the development of team-work in the operating room. Special care included a water balance in dehydrated cases, vitamin requirements, and anticipation of special treatment in emergency cases.

H. J. SIMS.

PATHOLOGY

STRAUS, R. Infectious mononucleosis simulating acute appendicitis with description of a specific lesion of the appendix. Am. J. Clin. Path., 12, 295 (June 1942).

A case of infectious mononucleosis with abdominal symptoms and signs of acute appendicitis is reported, in which the appendix, removed at operation, showed a lesion of the lymphoid tissue which was identical with those of the lymph glands from cases of infectious mononucleosis. In certain sections the follicular architecture of the lymphoid tissue was lost and the dense, darkly stained lymphoid cells were replaced by a mass of pale cells with large, pale, vesicular nuclei. These cells were ex-

tremely polymorphic. They measured 10 to 25 micra in long diameter, and were identical with similar cells in the lesions of the lymph glands in infectious mononucleosis which are considered pathognomonic of that disease. In the appendix of a second case simulating acute appendicitis and operated upon, these lesions were not found.

N. W. JONES.

PHYSIOLOGY

SECRETION

DAVISON, W. C. Difficulties in the enzymic titration of duodenal contents. Bull. Johns Hopkins Hosp., 70, 504 (June 1942).

Davison discussed the difficulties encountered in the enzymic titration of duodenal contents. He tabulated 12 factors which are often responsible in the inaccuracies in the reports of the enzyme activity of duodenal contents: (1) calculation of enzymic units; (2) enzyme method; (3) the amount and dilution of enzyme; (4) variations of degrees in temperature; (5) substrates; (6) the end-products of the reaction; (7) accelerators and paralyzers; (8) light and radiation; (9) the calibers of the capillary tubes; (10) the position of the collecting tubes in the duodenum; (11) the presence of gastric contents, and (12) changes in enzymic activity.

H. J. SIMS.

MOTILITY

INGELFINGER, F. J., AND MOSS, R. E. The activity of the descending duodenum during nausea. Am. J. Physiol., 136, 561 (June 1942).

Nausea was produced in human subjects 13 times by thermal stimulation of the labyrinth and 5 times by morphine sulfate administration. In 13 of these instances, a generalized contraction of the descending duodenum was recorded during nausea. The contraction of the descending duodenum often expelled both balloons backward into the stomach, although no reverse peristalsis was observed. It is suggested that duodenal spasm is a frequent concomitant of nausea, and that this spasm pushes the duodenal contents into the stomach by reversing the intestinal gradient. Necessarily, absolute pylorospasm during nausea would then be impossible.

ARTHUR E. MEYER.

METABOLISM AND NUTRITION

LANE, R. L., JOHNSON, E. AND WILLIAMS, R. R. Studies of the average American diet. I. Thiamine content. J. Nutrition, 23, 613 (June 1942).

The thiamine content of the average American diet, such as was consumed by the middle two-thirds or three-fourths of the population prior to the advent of enriched bread and flour, is about 0.8 mg. per 2500 calories. This is substantially lower than previously supposed from the results of computations such as those of Stiebeling and Phipard. If the use of enriched flour and bread becomes universal, the average intake will be increased about 64 percent to about 1.3 mg. per 2500 calories. Thiochrome assays of cooked flesh foods tend to give low values for thiamine on account of incomplete extraction. This error probably has a significant effect only on the thiamine contribution of lean pork to mixed diets. Desiccated flesh foods may give much too low thiochrome assay values. The principal contributors of thiamine to prevailing diets are lean pork, bread and milk. Tables are given to permit approximate calculation of thiamine yields of other diets as cooked and served.

ARTHUR E. MEYER.

MISCELLANEOUS

FLEXNER, J. AND BAUM, OTTO. Gastroscopic observations in pulmonary tuberculosis. Am. J. Med. Sciences, 204, 101 (July 1942).

In pulmonary tuberculosis Cullen found at autopsy only 4 cases of tuberculous involvement of the gastric mucosa in 1043 cases. Renander recently reported 2 cases of proven tuberculosis of the stomach and reviewed the small number of reported cases. No gastroscopic observations in tuberculous patients have come to the attention of the authors and they gastroscoped 26 patients successfully with pulmonary tuberculosis. Normal gastric mucosa was found in 5 pa-

tients. Chronic superficial gastritis was found in 7; chronic atrophic gastritis in 3; and a combination of these lesions in 10 patients. Chronic hypertrophic gastritis was seen in only one patient. Ulcers, tumors and tuberculous lesions were not observed. Mucosal bleeding was seen in 3 of the patients with chronic superficial gastritis. The 5 patients with normal gastric mucosae had no gastric complaints except anorexia. 10 of the remaining 20 patients had diffuse involvement of the gastric mucosa of a moderate to a marked degree but only 3 had gastric symptoms, while 6 of the 11 patients with only patchy, mild to moderate, mucosal involvement had gastric complaints. Symptoms occurred in 6 of the 10 patients having both chronic superficial and atrophic gastritis. The 1 patient with chronic hypertrophic gastritis has no gastric complaints. Tubercle bacilli were present in the sputum of all but 3 patients. Of 19 patients only 7 had free hydrochloric acid in the fasting specimen. In 9 patients the gastric residue was examined for tubercle bacilli which were present in 5, 3 of whom had free hydrochloric acid in the specimen.

ALLEN A. JONES.

NORRIS, J. L., BLANCHARD, J. AND POVOLNEY, C. Regeneration of rat liver at different ages: metabolism of embryonic, neonatal and regenerating rat liver. Arch. Path., 34, 208 (July 1942).

As liver tissue has a marked capacity to regenerate after partial hepatectomy, the authors studied the effect of varying ages on the rate of regeneration of liver tissue in rats. A total of 92 albino rats was used, divided into three groups; namely, those of less than 100 gm. weight, those weighing 100 to 250 gm. and an older group weighing over 250 gm. Sixty-five percent of the weight of the liver was removed in each animal.

Regeneration of liver following partial hepatectomy in the three age groups was compared and the metabolism of embryonic, neonatal and regenerating rat liver studied, the latter by determining the aerobic and anaerobic glycolysis, oxygen consumption and carbon-dioxide production. They determined that rat livers of all ages regenerate rapidly after partial hepatectomy but the rate and the total amount of regeneration varied inversely with the age of the animal. The rate of anaerobic glycolysis of regenerating liver was not increased over that of the normal resting liver in rats of comparable age and was independent of the length of time following partial hepatectomy and of the total amount of regeneration. The rate of anaerobic glycolysis of embryonal rat liver was higher than that of normal adult liver. The higher rates were correlated directly with the amounts of hemapoietic tissue in the liver at these periods. The increase in anaerobic glycolysis of neoplastic tissue over that of non-neoplastic tissue is due to differences inherent in and characteristic of two types of tissue and not to an increase in growth rate.

N. W. JONES.

MOORE, R. A., HELLMAN, L. M. AND JACOBIUS, H. Effect of parabiosis on the hepatic changes following obstruction of the common bile duct in rats. Arch. Path., 34, 196 (July 1942).

It was recently shown by Lieber and Stewart and McMahon and Mallory that there is in man a definite entity of obstructive biliary cirrhosis in the absence of infection. The extra hepatic obstruction caused dilatation of the smaller bile ducts, which filled with an inspissated brown material, presumably bile, which led to necrosis of the hepatic cells, epithelial proliferation and fibrosis.

In the present experiments rats were united in parabiosis. Five days later the common bile duct of the right hand member of the pair was ligated and divided: the bile ducts of control animals were obstructed in like manner. In the joined animals products of biliary secretion were eliminated by the normal animal after ligation of the common duct of the other. There appeared no jaundice and no accumulation of bile pigment in the liver of the latter animal, but the ducts became dilated and filled with a clear colorless secretion. Necrosis of the liver occurred in both parabiotic and control animals, and subsequently fibrosis, although more rapidly in the control. After

twenty days no difference was noted in the severity of the lesions. The presence of retained bile in the control animal with jaundice increased the necrosis but was not a necessary factor. The combined results suggested that the early phases of fibrosis and proliferation of the bile ducts were associated with the retention of bile, but the later changes were related to simple dilatation.

N. W. JONES.

COMPTON, A. Bacteriophage treatment of bacillary dysentery. Brit. Med. J., 719 (June 13, 1942).

The article is a presentation of the experience gained during 12 years in Alexandria in the use of bacteriophage in the treatment of bacillary dysentery. Between 1928 and 1940 the annual number of cases of both amebic and bacillary dysentery reported in that city was about 650 with little tendency for the number to decrease. During that period the dysentery mortality dropped from more than 20 percent to less than 6.5 percent. Since the ratio of bacillary dysentery to amebic dysentery remained unchanged, it is argued that the drop in mortality is the result of the introduction and use of phage therapy, for the bacillary variety. The city of Cairo, in which phage is not used, had an average mortality of 29 [illegible] from dysentery (probably both [illegible] from 1936 to 1938. This figure is [illegible]ted as further indication of the value phage. Only the most meager details [illegible] given of the therapeutic procedure followed.

HENRY TUMEN.

ERCHANT, A. K. Roentgen diagnosis of [illegible]ungous infections of gastro-intestinal tract. Radiol., 38, 660 (June 1942).

[illegible]chant reports several cases from the [illegible]n [illegible] which showed actinomycosis of [illegible] intestinal tract. Below the mouth the [illegible]ive system is very rarely involved by [illegible]gous infections. It is astonishing that h lesions are so rare. Some cases of [illegible]omycosis of the secum are reported. [illegible]s are difficult to differentiate roentgen[illegible]y from tuberculosis or carcinoma. The presence of a sinus or fistulous tract should make one suspect actinomycosis, and presence of the characteristic "sulphur granules" is of course pathognomonic.

FRANZ J. LUST.

CURRY, J. J., GREENWALT, T. J. AND TAT, R. J. Familial nonhemolytic jaundice. New Eng. J. Med., 226, 909 (June 1942).

Dameshek and Singer recently designated as "familial non-hemolytic jaundice" a group of cases of mild acholuric jaundice of familial incidence in which, although the van den Bergh reaction was "indirect", evidences of increased hemolysis (such as spherocytosis, increased hypotonic fragility, and increased fecal urobilinogen output) were lacking. Numerous liver function tests were negative with the exception of the bilirubin excretion test which showed abnormal retention.

The present authors report a case of familial non-hemolytic jaundice in a 50 year old man, in which jaundice had been noted since birth. All the classical features of the disease were present: "indirect" bilirubinemia between 3.0 and 12.6 mg. percent, no increase in hypotonic fragility, normal results in numerous liver function tests, absence of anemia, spherocytosis, and reticulocytosis, and low fecal urobilinogen excretion. The bilirubin excretion test was unsatisfactory because of the high serum bilirubin level. The patient also exhibited typical hematological effects following splenectomy (performed 19 years before): leukocytosis with lymphocytosis, occasional target cells and Howell-Jolly bodies, increased hypotonic resistance, an excessively low fecal urobilinogen output. Liver biopsy obtained at laparotomy revealed no evidence of hepatic disease. Examination of the sections of spleen showed no evidence of hemolytic or splenic disease. A jaundiced sister of the patient exhibited the features of familial-non-hemolytic jaundice, also.

The case is noteworthy because of the normal liver biopsy in a typical example of familial non-hemolytic jaundice. The inability of splenectomy to alter the course of the disease and the necessity for a clear differentiation between familial non-hemolytic

jaundice and congenital hemolytic jaundice are emphasized.

H. H. LERNER.

WHITE, J. AND EDWARDS, J. E. Effect of dietary cystine on the development of hepatic tumors in rats fed p-dimethylaminoazobenzene (butter yellow). J. Natl. Cancer Inst., 2, 535 (June 1942).

The percent incidence and the time of appearance of hepatic carcinomas in rats fed Butter Yellow (p-diaminoazobenzene) depends largely on the basic diet. This accounts for a number of opposed findings from various laboratories.

White and Edwards tested the effects of diets with high and with relatively low cystine contents. After 200 days of a high cystine diet and Butter Yellow; 96 percent of the rate had hepatic carcinomas, while only 15 percent of the animals on the low cystine diet and Butter Yellow has such tumors. After 390 and 500 days, the rate of incidence of tumors increased to 60 percent in the latter group. Thus, the effect of a low cystine diet seems to be mainly an increase of the latent period, rather than prevention of tumor formation.

H. NECHELES.

GREENSTEIN, J. P. AND STEWART, H. L. Note on the enzymatic activity of the transplanted adenocarcinoma of the mouse stomach. J. Natl. Cancer Inst., 2, 631 (June 1942).

Enzyme content of the normal gastric and intestinal mucosae, and of transplanted adenocarcinomas of the fundic mucosa (i.e. the pyloric stomach), and of the intestinal mucosa of the mouse were compared. The tumors were third, fourth, and eighth generation transplants of original methylcholanthrene induced adenocarcinomas of the stomach and of the small intestine. The gastric tumor did not possess peptic, rennin, or alkaline phosphatase activity, whereas the normal gastric mucosa is rich in these enzymes. The intestinal tumor did not possess alkaline phosphatase activity, which is abundant in the normal intestinal mucosa. Thymonucleodepolymerase was contained in both tumors as in normal gastric and intestinal mucosae. Certain enzymes thus disappear when tissues become malignant, while others stay.

H. NECHELES.

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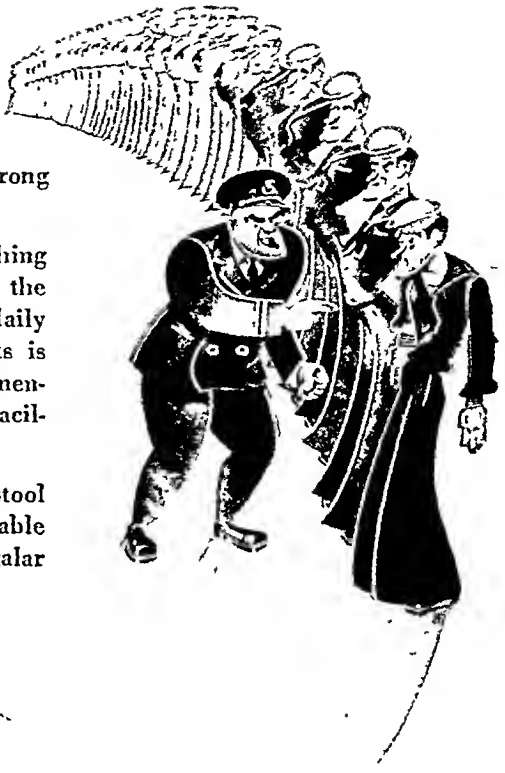

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